MEETING

STATE OF CALIFORNIA

AIR RESOURCES BOARD

SCIENTIFIC REVIEW PANEL

HOLIDAY INN

275 SOUTH AIRPORT BOULEVARD

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SOUTH SAN FRANCISCO, CALIFORNIA

FRIDAY, MAY 16, 2008

9:15 A.M.

JAMES F. PETERS, CSR, RPR
CERTIFIED SHORTHAND REPORTER
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APPEARANCES

PANEL MEMBERS

Dr. John Froines, Chairperson

Dr. Paul Blanc

Dr. Craig Byus

Dr. Gary Friedman

Dr. Stanton Glantz

REPRESENTING THE AIR RESOURCES BOARD:

Mr. Jim Behrmann, Liaison

Mr. Peter Mathews

REPRESENTING THE DEPARTMENT OF PESTICIDE REGULATION

Dr. Joseph Frank, Senior Toxicologist

Mr. Randy Segawa, Senior Environmental Research Scientist

REPRESENTING THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Dr. George Alexeeff, Deputy Director

Dr. Joe Brown, Staff Toxicologist

Dr. Melanie Marty, Chief, Air Toxicology and Epidemiology Section

Dr. Karen Riveles, Associate Toxicologist

Dr. Andrew Salmon, Chief, Air Toxicology and Risk Assessment Section

Dr. Brice Winder, Staff Toxicologist

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PROCEEDINGS

CHAIRPERSON FROINES: So let's call the meeting to order, the May 16th, 2008, meeting of the Scientific Review Panel.

And the first topic on the agenda is the --

PANEL MEMBER GLANTZ: There's some feedback. Can you --

CHAIRPERSON FROINES: Is that better?

PANEL MEMBER BLANC: It's Froines' wall of sound.

(Laughter.)

CHAIRPERSON FROINES: It's barely past 9 o'clock and we're already into this.

(Laughter.)

CHAIRPERSON FROINES: Let's put the lid on it and we will be fine.

(Laughter.)

CHAIRPERSON FROINES: So the first item on the agenda is the discussion of the Panel's findings related to the Endosulfan report.

So essentially comments from the Panel.

There's one change, by the way. That is, that Toby pointed out that there's a sentence that says, "DPR regulations specify MOEs of greater than 100 to be health protective." And actually there's no regulation, so we --

just DPR considers MOEs of greater than 100 to be health protective. So that's that.

Gary.

PANEL MEMBER BLANC: Where is that?

CHAIRPERSON FROINES: It's on page 3, numbered under 9.

PANEL MEMBER FRIEDMAN: Well, I had sent in a couple of comments on a previous draft. And I appreciate that one of them was very well responded to in terms of putting -- the first draft just said there were scenarios where there's excess exposure. And now there's actually some description of what those are, and I appreciate that. But there's still something I don't -- there was another change I suggested, which was not made. And probably I don't understand it, but I'd like to just raise that question again.

Item number 7 on page 2, the last two sentences: The subchronic inhalation NOAEL of 0.194 milligrams per kilogram-day is the critical NOAEL for evaluating both inhalation exposures and seasonal inhalation exposures in humans." Then the next sentence I don't understand. "The estimated no-effect level (ENEL) of" -- the same number, 0. -- oh, it's 0.01. Pardon me. I thought from the last draft they were the same. But 0194 for chronic effects in animals is the appropriate value for evaluating chronic

inhalation exposures. That may answer the question, because -- no, I missed the -- so I guess my question was, isn't there supposed to be some kind of factor, you know, taking into account intraspecies variation and within species variation that would make one not look at the animal level but what would be derived from that for humans as the appropriate thing. But I guess I missed the extra decimal place and that's -- does that answer the question?

CHAIRPERSON FROINES: Um-hmm.

PANEL MEMBER FRIEDMAN: So if it's a tenth as great in animals, that's a level that we accept for humans?

CHAIRPERSON FROINES: As the value.

PANEL MEMBER FRIEDMAN: Yes. I mean we've always translated values in animals by various factors -- uncertainty factors into humans. But now it just says here's the value for animals and that's what we accept for evaluating chronic inhalation exposures in humans.

PANEL MEMBER BLANC: I think -- I see now your confusion. I think it's because of the use of the word "for". And I think it should be based on --

CHAIRPERSON FROINES: That's right.

I'm sorry.

PANEL MEMBER BLANC: Do you think that's correct?

CHAIRPERSON FROINES: Um-hmm.

PANEL MEMBER BLANC: So I would suggest that if it read, "The estimated no-effect level of 0.194" -- "0.0194 milligrams per kilograms-day based on chronic effects in animals" --

OEHHA DEPUTY DIRECTOR ALEXEEFF: It's not based on the --

PANEL MEMBER BLANC: It's not based -- isn't it one-tenth of what the animal level is?

OEHHA DEPUTY DIRECTOR ALEXEEFF: Maybe -- George Alexeeff of OEHHA.

No -- Joe Frank, is he here?

Okay, yeah. So he can correct me if I'm wrong. But when you have -- this is the terminology that DPR uses -- estimated no-effect level, that means they've -- they didn't have an exact -- there was not an exact study of a no-effect level. So it's estimated by adding in an uncertainty factor or an adjustment factor.

So they've simply taken the subchronic value, added a tenfold adjustment factor, and estimated the chronic value. So it's still based on that same study, the same study as the subchronic study. Is that correct, Joe?

DPR SENIOR TOXICOLOGIST FRANK: That's correct.

OEHHA DEPUTY DIRECTOR ALEXEEFF: That is correct.

Does that -- so the reason that you estimated is because we did not have a study that specifically met the chronic criteria.

CHAIRPERSON FROINES: So we should say based on subchronic effects in animals.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

OEHHA DEPUTY DIRECTOR ALEXEEFF: Is that correct?

Yeah, that's correct.

PANEL MEMBER FRIEDMAN: So the previous sentence has just taken and added an uncertainty factor to that, is that -- of tenfold? Well, actually it's ten times as great. So I guess I still don't fully understand what's going on here.

PANEL MEMBER BLANC: No, it's ten times as sensitive, Gary. Ten times more sensitive, ten times lower.

PANEL MEMBER FRIEDMAN: But they're saying that a ten times as great level in the previous sentence is the critical for evaluating exposures in humans. So wouldn't you want an even lower level than what's observed as no effect -- or is estimated as no effect in animals?

CHAIRPERSON FROINES: That's the tenfold safety factor -- uncertainty factor.

PANEL MEMBER FRIEDMAN: But it seems to be going

in the wrong direction.

CHAIRPERSON FROINES: I don't think so.

OEHHA DEPUTY DIRECTOR ALEXEEFF: George Alexeeff again.

No, it's not going in the wrong direction. The extrapolation -- the adjustment is not from animal to human at this point. It is simply subchronic to chronic. So in this case it's still the same animal study and we're still ultimately trying to protect humans. But it's not an actual interspecies adjustment at this point. So it would --

CHAIRPERSON FROINES: That's how I understood it.

PANEL MEMBER FRIEDMAN: Well, I don't want to take up -- you know, I guess I don't fully understand it. But if everyone else accepts it, you know, that's fine. I'll just talk to somebody afterwards and better understand it.

CHAIRPERSON FROINES: It is -- the point is it is what it is, and it's the basis around which MOEs are calculated. And so the only -- what I would like -- what I think we would all like to avoid is getting into some explanation -- I mean we could add in, although I'm not sure I'm for it, but add in what George said, is that this is a subchronic to chronic adjustment.

We're saying the estimated no-effect level of

.0194 based on subchronic effects in animals is the appropriate value for evaluating chronic inhalation exposure in humans. So I think it's clear.

PANEL MEMBER BLANC: Yeah, with that change I think it's fine.

PANEL MEMBER FRIEDMAN: Okay.

CHAIRPERSON FROINES: You're okay?

PANEL MEMBER FRIEDMAN: I mean it's -- I don't want to take up more time of the Committee. I mean I respect you guys. And I just need to talk to somebody off line about it just for my own education.

CHAIRPERSON FROINES: Okay. George, what's the history of this term -- Randy -- what's the history of the ENEL? Because that's historically not the way we've talked about this?

OEHHA DEPUTY DIRECTOR ALEXEEFF: I mean the history is that -- I mean OEHHA has --

CHAIRPERSON FROINES: Randy may want to --

OEHHA DEPUTY DIRECTOR ALEXEEFF: Or Joe -- I think Joe Frank is probably the appropriate person, from DPR.

But the history is that we've always done this type of adjustment. DPR has always explicitly called it an estimate. And we just -- we never used that word. We just said the NOAEL is such and such. But in there there

might be an adjustment factor from a LOEL or a subchronic to chronic or something like that. They just explicitly state that it's -- we didn't have the exact study on which we got this number. We had to make an adjustment, so call it the ENEL.

CHAIRPERSON FROINES: It's just that I -- for me, and maybe this is my fading memory as I age, especially with this Panel, but I think the ENEL is a new term, isn't it?

PANEL MEMBER FRIEDMAN: Yes, I've never seen it before.

CHAIRPERSON FROINES: Is it? Because I --

OEHHA DEPUTY DIRECTOR ALEXEEFF: They've --

CHAIRPERSON FROINES: Well, give him a chance. He's with DPR.

OEHHA DEPUTY DIRECTOR ALEXEEFF: Yeah, Joe, why don't you just come on up and explain --

PANEL MEMBER GLANTZ: Why don't -- yeah, because I have the same reaction. Why don't you just delete the paren ENEL close paren. Then it's just an estimated no-effect level.

CHAIRPERSON FROINES: We could do that.

PANEL MEMBER GLANTZ: Then we don't have a new acronym introduced that's causing us all --

DPR SENIOR TOXICOLOGIST FRANK: Yes, I'm Joe

Frank from DPR.

It's something we've used for a number of years. And the reason we throw "estimated" in front of a NOEL is to just make it a little more clear that we're not using an actual calculated NOEL. But we've done that in the past as well. For example, when we don't have a NOEL, we have a LOEL, then we'll do an adjustment factor of 10 and call it an estimated NOEL. And some people just make it shorthanded and call it an ENEL. But it's an estimated NOEL with some sort of adjustment. And the rationale in the document should always be clear.

CHAIRPERSON FROINES: So, Stan, taking out the acronym is -- it is the estimated no-effect level.

PANEL MEMBER GLANTZ: Yeah. But the acronym, I had the same reaction. I never heard of ENEL for that.

It's not worth arguing about.

CHAIRPERSON FROINES: So, okay, let's -- I think there's agreement that this is -- these changes clarify a --

PANEL MEMBER FRIEDMAN: But, again, George was saying that what really the tenfold difference is from chronic to subchronic --

CHAIRPERSON FROINES: Subchronic to chronic.

PANEL MEMBER FRIEDMAN: Beg your pardon?

CHAIRPERSON FROINES: Subchronic to chronic.

You're taking a subchronic study and you're -- and you don't know if that's appropriate -- entirely appropriate for a chronic value. And so you're adding a safety factor of 10 -- uncertainty factor, whichever. In other words the subchronic study is not a chronic study. And so they're simply saying, "We're going to add an uncertainty factor of 10 to take that into consideration."

PANEL MEMBER FRIEDMAN: Okay. But we've always -- there's always been uncertainty factors when we go from one species to humans. And that last sentence seems to deny that.

PANEL MEMBER BLANC: But you're mixing apples and oranges, because in their system instead of doing that, what they do is this ratio of possible exposure to NOEL. And then they put the safety factor in after that essentially by saying that the -- if the margin of the ratio isn't a thousandfold or a hundredfold, then the potential for an effect is possible. And so that's how they do it in the DPR thing. That's what's confusing you, I think, is that that's where -- whereas in the other system we're used to where we're talking about action levels or whatever they -- I forget what they call it -- MACs or whatever the hell they are, that's where they start using those multiplication factors in that way. So that I think is what's essentially confusing you.

PANEL MEMBER FRIEDMAN: Well, what's confusing me is the appearance of the word "chronic" in the last sentence twice. "The estimated no-effect level for chronic effects in animals is the appropriate value for evaluating chronic inhalation exposures in humans."

CHAIRPERSON FROINES: We changed that. We changed it to: "The estimated no-effect level of .0194 milligrams per kilogram-day based on subchronic effects in animals is the appropriate value for evaluating" --

PANEL MEMBER FRIEDMAN: Okay, thank you. That takes care of it.

CHAIRPERSON FROINES: So --

PANEL MEMBER BLANC: I'll move to accept the findings as stated, with the modifications as noted.

CHAIRPERSON FROINES: Is there a second?

PANEL MEMBER FRIEDMAN: Second.

CHAIRPERSON FROINES: Is there discussion?

Hearing no discussion.

All those in favor of adopting the motion.

(Hands raised.)

CHAIRPERSON FROINES: Unanimous.

PANEL MEMBER BLANC: The Chair's voting too?

CHAIRPERSON FROINES: Sure.

So that's good.

I wanted to raise one issue with you and not

overstate it. But in this document, we are -- we are making findings that one could say at a minor level or a not so minor level, whatever -- however one wants to characterize it -- we are differing from DPR in our findings. And my view is that -- as you noticed, I didn't write anything to call attention to that in these findings. But I thought that it might be -- we shouldn't just leave it in that way. So I thought when I wrote the transmittal letter to Mary-Ann, that I would actually bring to her attention that there is a difference of opinion.

The other alternative is to just not mention it at all. But, for example, there was very -- there was very active discussion about the safety factor for children. And my view is that DPR should be aware that the Panel thinks that there should be a safety factor to take into account that particular issue.

So I assume that won't create any problems. But we can go either way. We can just ignore the differences in terms of our communication with DPR or we can call attention to it.

PANEL MEMBER GLANTZ: I think you should point it out in a cover letter.

PANEL MEMBER FRIEDMAN: I do. And specify what they are and not just say there are differences and people

have to search for them. But specify what you were just saying.

CHAIRPERSON FROINES: Yeah. It would be very brief. It may be just a couple, three --

PANEL MEMBER BLANC: That's on point 11, right?

CHAIRPERSON FROINES: Well, there are three issues --

PANEL MEMBER BLANC: But there's also the genotoxicity issue --

CHAIRPERSON FROINES: -- genotoxicity. And their document basically spends a lot of time saying it's not a carcinogen. And in true academic form we would prefer to say further studies would be relevant.

So there are three issues. I frankly don't understand why they -- every academic always says more research is needed, and that's all we were saying. And so the fact that they didn't adopt that seems to me to be unfortunate. But, again, it's not something to make a big deal out of, because I think that the history of Endosulfan is that it's on the way out. And so whether -- actually whether one wants to do chronic bioassays at a national toxicology program, that's -- whether it's worth it on Endosulfan is a good question.

PANEL MEMBER BLANC: No, but it has to do with what criteria one might use to assess genotoxicity.

CHAIRPERSON FROINES: Right.

PANEL MEMBER BLANC: And I think that there was -- I think the emphasis you might put on that in the letter is that we perhaps lean more towards a holistic assessment of genotoxicity, without using carcinogenicity as the trump card. In other words, I -- I mean if I had to summarize the discussion around the table, it was, yes, okay, the carcinogenicity studies are weak. But because those studies were equivocal in the face of other studies that are convincing of genotoxicity short of carcinogenicity, it's important to not discard that, which seemed to be less equivocal, the evidence. So I think that would be a sort of positive spin to put on it. Not that we thought that they should have said it was a carcinogen, but that there were studies that would have seemed to put it more squarely as genotoxic even if you couldn't establish carcinogenicity.

CHAIRPERSON FROINES: Well, in fact, that's what our finding says. We say, "The Panel has concluded Endosulfan is likely genotoxic." We acknowledge that "Endosulfan has not consistently induced tumors in rats and mice. However, due to its genotoxicity and tumor-promoting ability, Endosulfan has the potential to be carcinogenic with further studies required."

That seems to me to be --

PANEL MEMBER BLANC: Yeah, yeah.

CHAIRPERSON FROINES: -- exactly what you're saying.

PANEL MEMBER BLANC: Right.

CHAIRPERSON FROINES: And in the transmittal letter you're saying --

PANEL MEMBER BLANC: Right, exactly.

CHAIRPERSON FROINES: So with the changes that we just made, we are finished on Endosulfan.

So, Randy, I'll write a transmittal letter next week and send it over to you guys. And Kathy and --

PANEL MEMBER BLANC: -- Joe.

CHAIRPERSON FROINES: -- Joe got it down to three pages. I got it back to four pages with Gary's comments. But this may be a new record. Probably is a model.

We finally after how many years, Gary, have gotten to you're argument of --

PANEL MEMBER FRIEDMAN: No. Well, you got it back to the way it used to be.

CHAIRPERSON FROINES: No, it's only four pages.

PANEL MEMBER FRIEDMAN: Oh, yeah. But that's what it -- that's good. I mean I --

PANEL MEMBER BLANC: Oh, you're saying that's good.

PANEL MEMBER FRIEDMAN: Yeah. I mean the first

report we got was huge. And so this is just right.

CHAIRPERSON FROINES: I wonder how many pages we had with diesel? Do you remember, George? I'm sure it wasn't four.

(Laughter.)

CHAIRPERSON FROINES: Melanie, we'll move ahead.

(Thereupon an overhead presentation was Presented as follows.)

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Good morning. Melanie Marty.

PANEL MEMBER BLANC: Good morning, Melanie.

PANEL MEMBER GLANTZ: Morning, Melanie.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So this morning we're going to be going over our revised methodology for non-cancer risk assessment. And as you'll recall, the Panel got first the public review draft to look at while we were busy responding to public comments. And then once we did that, the Panel received our revised version plus the responses to comments for their review.

So what we're going to do today is go over, first, the methodology section, which is the big part of the document, and then individually the chemicals that we developed Reference Exposure Levels based on the revised methodology.

So I'm going to have Andy present the technical support document and the main -- just the main issues. And we had given a presentation at the last SRP meeting, so we didn't want to just repeat that whole thing. So we're going to again hit the highlights and then focus on a few changes that were made, including changes in response to the lead on the methodology section, who is Dr. Glantz. So --

CHAIRPERSON FROINES: Could I do two things.

First is, Randy, just before we get off DPR, in terms of planning for future meetings, do you have a sense of when the next pesticide will come to the Panel? And if you don't, that's fine.

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST SEGAWA: Good morning. I'm Randy Segawa with the Department of Pesticide Regulation.

The next chemical we think will be chloropicrin and will probably come to you this fall, is our hope.

CHAIRPERSON FROINES: Fall.

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST SEGAWA: Yes.

CHAIRPERSON FROINES: It would be September or closer to December?

DPR SENIOR ENVIRONMENTAL RESEARCH SCIENTIST SEGAWA: I would say closer to December.

CHAIRPERSON FROINES: Okay. So that will affect our planning.

Thank you very much.

Melanie, since we just went through the findings, historically we've never -- we've voted on issues like this, but we've not written findings. Is that your general view of this? Do you want findings from the Panel?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: You're right, that historically for these documents you have not written findings. The findings have only been for identification of a chemical as a toxic air contaminant.

If you want to write findings, it's up to you guys. But we didn't anticipate that you would.

CHAIRPERSON FROINES: Well, here's what I think -- and I'm certainly willing to be a minority. But that I've become aware that throughout the world and within the United States that there are a lot of agencies and groups that actually pay attention to what OEHHA is doing. And so you've been -- you are a leader both in terms of the risk assessment values that you derive but also in the risk assessment methodology to lead to those values.

So there's a lot of attention to OEHHA's findings

in a very wide spectrum of organizations and groups. And so my sense would be that having a very short couple of sentence, a page even, findings in which an established scientific panel blessed what you have done would reinforce the credibility of your effort. So my sense would be that it would be valuable -- it might be helpful, not necessarily valuable, to have short findings.

What do you think about that?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That's a good point.

CHAIRPERSON FROINES: Stan, what do you think?

PANEL MEMBER GLANTZ: Well, I always sort of thought that the fact that it was approved -- the report was approved by the Panel was all you needed. But I don't see any harm in it. And I'd be happy to work with Melanie to prepare some brief findings.

CHAIRPERSON FROINES: I mean I think it should be brief and --

PANEL MEMBER GLANTZ: No more than 12 pages.

(Laughter.)

CHAIRPERSON FROINES: Do you want to write 12 pages?

PANEL MEMBER GLANTZ: No, no, no. No, I think that -- you know, that would be like an executive summary almost. But, yeah, if you think that's a good idea, I

don't think that would be hard to do.

My only thing was I didn't know if we were going to -- my predilection is that we should approve the parts of the report that are here today.

CHAIRPERSON FROINES: Yeah, we'll get to that.

PANEL MEMBER GLANTZ: So I mean creating a findings document, would that in any way delay anything? That would be my only concern.

CHAIRPERSON FROINES: I don't think so.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Just a reminder. We do have another meeting scheduled for June 18th. So things that carry over, we can --

CHAIRPERSON FROINES: And I asked Melanie today is there enough substance for a meeting a month from now? And she assured me that there was. So we'll go ahead with the planning.

I think that Melanie said that manganese is probably going to elicit a lot of interesting comment. And Paul Blanc is just waiting with bated breath on manganese, I know.

PANEL MEMBER GLANTZ: Okay. Well, I'd just say -- I mean I don't know -- I can't prejudge what the Panel's going to do. But I'm happy with the methodology part of the document now. So I would hope we would be

able to approve it today. Although if people raise issues, then we won't. But I suppose we could approve the document and then approve an additional set of findings in a month.

CHAIRPERSON FROINES: Anyway, let's go ahead.

--o0o--

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Is this okay?

Yeah, I think so.

Okay. I'm Andy Salmon with OEHHA.

As Melanie said, I've got a short presentation here which just picks out some of the highlights of the document.

--o0o--

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: You saw the previous draft version there of course. And this version which you have received is in response to comments -- first round of comments from particularly Dr. Glantz. And also we now do have the public comments assembled, and we have responses for those, which you also have.

I'm just going to provide a very brief summary here. But obviously if there are any points either in that or during the rest of the presentation that you want to amplify, then please do so.

The key factors here are, firstly, that we needed to revise the non-cancer risk assessment guidelines to respond to SB 25, the Children's Environmental Health Protection Act, and to make methods specifically responsible to sensitivities of children.

The other thing which has happened is that in the intervening ten years or so since we did the previous round of these guidelines there have been a number of significant scientific developments which we needed to incorporate.

So I'll just briefly review. But I'm basically going through the things which are different from the old guidelines as a summary here.

--o0o--

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Firstly, children are explicitly identified as a critical target population.

A second principle is that, although we continue to use the uncertainty factor approach in the risk assessment out of necessity, nevertheless when possible we will replace uncertainty factors with explicit models such as the preferred use of pharmacokinetic models for inter and intraspecies extrapolation.

Another thing --

CHAIRPERSON FROINES: Andy, can I ask you a

question?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Certainly.

CHAIRPERSON FROINES: Going back a long time ago when we did methylene chloride, I remember George's presentation where he went through all the uncertainties in the PVPK models. And we've come a long way since that time and obviously the models are much more accepted. But there's still some -- in my view, some ambiguity about the uncertainty associated with them.

And in terms of the models, I assume that you spend a fair amount of time looking -- still to this day looking at those uncertainty issues, because they are rampant I think.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Absolutely. I think that the standard practice in using pharmacokinetic models now definitely includes things like sensitivity analysis. And we have in fact used things like, you know, a Monte Carlo distributional analysis in some of the models. Exactly how explicit that is in the narrative about the model is a little bit variable, because there's an underlying principle that some degree at least a basic sort of -- at least an informal sensitivity analysis to figure out whether we know enough to make use of the model.

And of course one of the things about the uncertainties that you uncover in the use of the model is that these are all -- it may look as if the model is making things worse rather than better. But what it's actually doing is pointing out that your previous assessment based on an uncertainty factor didn't necessarily cover all the variables adequately. So I think even if a model in fact displays some relatively large and serious uncertainties, it's still a useful way of looking at the situation, or at least that's the general analysis which we're offering in this document.

So, obviously, you know, when it comes to a particular assessment, then everything is case by case and we either do or do not use the model depending on whether it's reasonable, appropriate and sufficiently -- we're sufficiently confident in it.

CHAIRPERSON FROINES: And I'm embarrassed to say that I've forgotten whether what you just said verbally is actually in the document.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I believe it is, yes.

CHAIRPERSON FROINES: So, that's okay. I just think it -- the issue of sensitivity and uncertainty I think just need to be explicitly stated that you -- so nobody has any illusion that you just accept the --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, certainly I think, you know, we do take that as a point. And, you know, we'll go through and check to make sure whether -- see whether there isn't something we ought to underline in the document. But I believe that statement is there. But we'll check to make --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We'll cheek.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: -- we'll check to make sure that it's sufficiently emphatic.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I think it's safe to say that nobody thinks that PBPK models erase all uncertainty.

CHAIRPERSON FROINES: Well, but the other side of it is when you get into Monte Carlo simulation, then of course the number of options you have becomes this monster. And so --

PANEL MEMBER GLANTZ: Well, yes and no. I mean you can -- the value of doing the Monte Carlo simulations, you can introduce uncertainty and a whole bunch of parameters in the model, but at the end you have one number popping out at the end. And so what you end up with is the distributional characteristics of the net

result. In this case it would be the REL.

So the fact that there's a lot of -- a lot of uncertainty in different elements of the model, what you end up with is the net effect on the output variable. So what you end up with is just some measure of uncertainty in what the REL is. There's this sort of cumulative effect of all the other uncertainties.

CHAIRPERSON FROINES: Well, but with the -- if you look at some of Dale Hattis's work, and he gives you a list of options to choose from that's, you know, pages long, and his input. And what he is saying is that there then needs to be a decision about what you intend to adopt.

PANEL MEMBER GLANTZ: Sure. But that's true in anything.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah, I think one of the problems which you inevitably face with this sort of modeling approach is that, you know, on the one hand you've got things which are essentially variability, where you can relatively easily at least -- you know, you can get some idea of what the distribution of the variability is likely to be. And, you know, following Dale Hattis of course we tend to assume it's not normal. But at least, you know, that you have some kind of a handle on the issue with that.

Whereas, that contrasts with the problems of model uncertainty, which you can produce essentially a dichotomous uncertainty distribution. And at some point we have to say, well, we're going to take a more conservative assumption, because the risks of being wrong -- if we choose the less conservative assumption and we're wrong, there's a substantial risk to public health involved. So, you know, at some point we have to step away from trying to be too mathematically clever and simply take a public health protective decision. And I think that is a -- you know, that's an enshrined principle, so...

CHAIRPERSON FROINES: Yeah, I think -- yeah, I agree that Dale looks at variability in the -- go ahead. I'm sorry.

--o0o--

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Okay. Just a minute. Did I -- yeah, I need to talk about this slide.

Yeah, we're also proposing to include an 8-hour REL. This is something we've actually been asked to do by some commentators. And this is something which has an -- it's specific to an 8-hour time-weighted average exposure. It may be repeated for an ongoing situation. But if it was a real lifetime exposure situation,

obviously we'd use the chronic REL. But this covers certain particular situations such as off-site workers, children in schools, and some other special situations which apply in some Hot Spots risk assessments.

We're considering also, again in response to comments we've received, that we may in cases where it's needed develop separate values for adults and for infants and children because of the nature of the special situations that the assessments might be facing.

The 8-hour reference exposure levels which you see in the package, and which we'll be talking about in a few minutes, are designed to be protective of children. But we are considering the possibility in the future of developing ones which would be protective of adults but not children as a later development.

PANEL MEMBER BYUS: Yeah, I have a comment -- shall we comment now or -- as we go along or --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Go ahead.

PANEL MEMBER BYUS: I had one comment in regard to that last statement. And, that is, you've done a very nice job for the most part about children. But the other major variable is the geriatric, older, elderly.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes.

PANEL MEMBER BYUS: And in terms of pharmacokinetics, toxicokinetics it's even -- potentially even more dramatic than the difference between adult and children is the difference between geriatric and adult. As you know, clearance -- virtually all the clearance mechanisms are significantly reduced in geriatrics as you age: Renal clearance, secretion, filtration markedly diminished; lung capacity's markedly diminished; distribution effects or cardiac output is significantly reduced. So in terms of toxicokinetics and then the SIP enzymes, there's a both quantitative and qualitative difference among geriatric patients -- or geriatrics, not patients -- drugs here.

The other difference is disease -- the disease overlay. As you age, you have much more likelihood to have disease processes which could affect your sensitivity for the toxicodynamic aspects. Environmental exposures.

And also geriatric -- elderly are usually taking a lot more drugs, so their clearance mechanisms can be saturated in terms of environmental.

So really, you know -- and I think somewhere in here you should mention this. Now, whether you want to discuss it in detail, but I think you should mention it because it's sort of strikingly absent as you read it. And I like the way this is written and I like the way it's

done -- don't get me wrong -- for the most part. But I think it's -- when I read it, that's what I was struck by.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We will add a paragraph. I think that's a good point. There is some effort underway in the risk assessment community to try to get a better handle on that, because it's absolutely true.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I think we do say somewhere that we -- you know, we have a concern for sensitive sub-populations of any type, of which children obviously are an example. But we should make --

PANEL MEMBER BYUS: But then the drug analogy which you've used in here. And the drug analogy, there's much more data on a geriatrics, there's much more interest in it, and there's much more information available. So in a sense I think it would almost be easier than to do the children. But not that the children are not important, because it is, very clearly.

But, as I said, it's strikingly not stated. You should at least have a paragraph. Say what I just said and that your more detail analysis will come later. Because I think because it's not said here, it's like maybe you're not aware of it and that it makes your other arguments about the children less valid.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We'll add a paragraph. Also, Dale Hattis has done some work looking just exactly at that.

CHAIRPERSON FROINES: Yeah, but it -- Melanie, I think that's a really important point that is not really going to be dealt with by a paragraph in the long run; in the short run perhaps. But in the long run it seems to me that we ought to develop a project on geriatric --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, as Melanie says, there is in fact some ongoing investigation into this area going on inside of OEHHA; not specifically in this context but in general. So you will likely be seeing some product or response to that at some point.

CHAIRPERSON FROINES: It would be interesting to actually do a worst-case scenario and, say, look at, you know, these chemicals being blocked because you're metabolism is -- your clearance is saturated and so on. And I don't want to get into --

PANEL MEMBER BYUS: But, as you say, clearance is the -- clearance is what allows drugs and chemicals to accumulate. So if clearance is impaired, that's like the worst thing that could happen for accumulation. I mean exposure -- repeated exposure is important, but its clearance is the controlling factor. And because

clearance is generally decreased in all aspects in the geriatric patients, plus the disease sensitivity, toxicodynamic aspect, you know, because they would be much more likely to have any of a variety of overlaying diseases than you would be in a child, it really -- you know, and it struck me as I was reading it, and just what you just said, that geriatrics people could be the most sensitive out there in the environment.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, you know, it's certainly true for particulate matter air pollution, among other things. I mean, you know, we can see that in Epi studies.

PANEL MEMBER BYUS: Sure.

PANEL MEMBER GLANTZ: Do you have any specific references you think they ought to --

PANEL MEMBER BYUS: I was going to give you a reference site. There's actually a very good paper, I think it was in Nature about four or five years ago -- that has -- I use it in my lectures to medical students. It has great graphics about the changes in the SIP enzymes' clearance, from child through adult to geriatric. They show you the continuum. It's a very nice series of graphics. And I can get you the reference for that.

CHAIRPERSON FROINES: Okay. That would be great. Thank you.

PANEL MEMBER FRIEDMAN: Would you send it to all of us?

PANEL MEMBER BYUS: Sure, sure.

PANEL MEMBER FRIEDMAN: Thank you.

PANEL MEMBER GLANTZ: It's becoming more relevant every day.

(Laughter.)

PANEL MEMBER BYUS: Shocking though. That's why I -- I keep looking at those diminished organ capacities with age. And it's a wonder I can even walk and go to the bathroom properly.

(Laughter.)

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The next thing I was just going to mention in passing is this idea that the inter and intraspecies uncertainty factors originally were just -- you know, they're ten because we have ten fingers, and they were considered as a monolithic item. But more recently people have started to think of both of these uncertainty factors as consisting of both a pharmacokinetic and a pharmacodynamic component. And the advantage of doing that is, firstly, it gives you a slightly more refined way of deciding whether the value you're using is sufficient; and, secondly, it gives you the opportunity to individually replace these with specific models. Whereas

is often the case, one might, for instance, have a pharmacokinetic model which was compound and species specific but not of a dynamic model -- not a model toxic response.

--o0o--

CHAIRPERSON FROINES: Do you think -- Do you think -- sorry. Going back to that.

Do you think that you are going to have enough information on pharmacodynamic issues?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I was just going to add that --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Seldom.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, exactly. That's going to be really rare. And I can't think of an example that actually exists right now where we're confident that the pharmacodynamics is adequately modeled.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: It's possible that the OP people might be able to do something. But I don't think we want to go there at this point.

CHAIRPERSON FROINES: I mean the toxicokinetics is much simpler. That's --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: It's better understood at least.

CHAIRPERSON FROINES: It's better understood. Simpler's not the right word. But you know what I mean.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Yes. I would certainly agree with that in general.

The other thing we've talked to you about already at some length is the use of benchmark concentration methodology. And this we now prefer -- when we can use it, which is actually most of the time, we prefer the benchmark concentration approach. And we specifically define our benchmark or point of departure so that it has properties which are similar to a NOEL, so we would be using the same uncertainty factors with that point of departure as we do for a NOEL.

CHAIRPERSON FROINES: As we move into the new era, however rapidly it emerges, when we are going to be using, quote, biomarkers and high throughput assays and all the other things that were in that NRC report that Lauren Zeise was on, as we get into that, then the issue of a threshold becomes much more difficult because you're looking at changes in NRF keep-one, you know, changes or oxidated stress or whatever the -- glutathione depletion -- you begin to have the potential to look at things for which there is, if anything, a very low

threshold. And so you'll have data that one could use at a very different stage in understanding the process. And I assume that that's going to affect everything.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes, I think it's safe to say it will affect risk assessment. And that at this point a lot of the people doing risk assessment are asking ourselves, how are we going to deal with those types of data? Not that we haven't dealt with them in the past before. Perchlorate is one example where our drinking water group based the public health goal on what was considered a precursor effect, that is, inhibition of iodine uptake by the thyroid.

So, you know, it is a very interesting problem. And it's going to -- it's going to require a lot of thought on how to apply this, because you're absolutely right, the meaning of a threshold is certainly going to change in that context.

CHAIRPERSON FROINES: Well, it's also going to require major policy and legal considerations. Because if you say that inhibition of various phosphatase is an adverse effect that you're going to regulate, you're going to end up in court with people saying that's a biochemical

marker, that's not a rat study.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Amen.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, yeah, there's a huge debate about this going on at the moment. I mean there are some actual technical approaches including one which you will see in one of the -- in the acetaldehyde REL coming up, where you can actually use a severity score for a particular response as an input to what essentially is a pseudo-continuous variable as input to a benchmark model.

So there are actually some technical measures we have in hand which will assist us in responding to that dilemma. But it certainly doesn't relieve us of, as you point out, the basic sort of policy-based decision as to how we're going to be able to respond to that.

CHAIRPERSON FROINES: I meant activation of phosphatase. It's not inhibition. So --

PANEL MEMBER BYUS: You mention in here about defining the effect as a toxicological effect, not a biological effect.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes.

PANEL MEMBER BYUS: I mean that's really where the argument is, are these markers biological or

toxicology -- toxicological? And the strength of that association is where the discussion will lie. And you do mention that in here, that -- and that when you set these values, you're looking at the toxicological endpoint as best that you can.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes.

CHAIRPERSON FROINES: So if you have activation of NRF2 and you're seeing more Phase 2 enzymes, is that a toxicologic effect? It's trying to prevent a toxicologic effect.

PANEL MEMBER BYUS: Not necessarily toxicological.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We don't necessarily --

PANEL MEMBER BYUS: You have to go further on that association.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah, it depends on what's going on. And there are certainly circumstances in which activation of Phase 1 or Phase 2 enzymes could actually have adverse consequences. I mean some of the -- actually some of the endocrine impacts of certain chemicals involve activation of enzymes which also degrade things like T3 or steroid hormones or whatever.

So, you know, just activating an enzyme sounds pretty harmless, but it isn't necessarily. So, needless to say, there isn't a simple answer.

But in general where the principle has always been that things which are successfully adaptive are considered a biological response, whereas something which represents an increase above normal of something which would be considered either a clearly harmful or a precursor indicator of the beginning of a harmful process would be regarded as a toxic response.

But, yes, it's a difficult decision. But somewhere at that point is where the -- point comes.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We did host a conference on what is an adverse effect. And we do have materials from that. If anyone's interested, we can send you a link.

CHAIRPERSON FROINES: Yeah, we should have that.

And of course -- and I'll shut up for a while before I get criticized.

I lost my train a thought. Go ahead.

(Laughter.)

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Okay. So I'll just run through our proposals on interspecies extrapolation.

The traditional value of the UFA, the interspecies uncertainty factor, has been 10, which we now regard by default as consisting of a toxicokinetic factor of root 10, or approximately 3, and a toxicodynamic factor again of root 10, or approximately 3. The reason for root 10 obviously is if you put two together, then you get the results of 10 because these are multiplicative factors.

PANEL MEMBER FRIEDMAN: May I ask, is the subscript A -- just to help me remember these subscripts, does that stand for animals?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, it does. A stand for animal, K stands for kinetic, and D stands for dynamic.

PANEL MEMBER FRIEDMAN: And H for human?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: H for human, yes. You'll see these coming through repeatedly, but that's the convention.

And as I mentioned previously, when we have the opportunity to do so, we would replace either one or both of these with a model. So if we have what we consider an adequate model, then we would drop, say, the kinetic factor. So you'd have an overall -- a UFA of 3.

But there's what we consider a partial model, which was being used quite a bit in the past, which is the U.S. EPA's health -- human equivalent concentration

calculation based on their regional gas dose distribution model, an RGDR model. That we regard as a partial model.

And so unlike previous practice, we're now actually just reducing the UFA to 6 rather than 3, because we don't see that model as covering all the kinetic uncertainties. It doesn't deal with metabolism. It doesn't deal with distribution outside of the -- and it's a fairly generic model of what goes on in the lung as well. But it's nevertheless useful when we don't have anything better.

And as we commented previously, unfortunately there are few cases where we have a workable toxicodynamic model. Although we may feel that we know enough about the toxicodynamic situation that we might feel we should choose a non-default value of the UFA-d if we know something about the dynamics.

And so in all these cases what we're recommending is defaults for which we can choose something different based on specific information that we might have.

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CHAIRPERSON FROINES: I worry a little bit about your only giving a factor of 3 for toxicokinetics. If you take Craig's comments earlier, the toxicokinetics could be much greater.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: That is particularly true of the intraspecies variability, which is what -- which is the next one I'm just about to speak to. And you will see that I heartily endorse your sentiments.

The big question for intraspecies toxicokinetic variability obviously is, is the previous use of the value of root 10 for UFH-k adequate to protect, well, children or other sensitive sub-populations. And the answer is, in our opinion, no. We have some specific reasons for thinking that based on particularly the studies in drugs where there's been a lot of work describing kinetics. And we refer particularly to work by Hattis and Ginsberg as well as several other authors. And also we did some work on our own account, which is reported in the Appendix E of the document.

And based on that, it appears an increase of UFH-k is necessary for many chemicals.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: And so what we're proposing is that the default value of UFH-k would increase to 10. Although obviously this would be varied, firstly, for chemicals which are not metabolized and which are having -- had a local site of action rather than distributed. In fact, there isn't very much pharmacokinetics going on there. So

we wouldn't propose the increase in that case.

And also in general, if we have a better model or we have some other reasons showing why some value other than 10 is appropriate in a specific case, then we would use that.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The toxicodynamic variability, as we have said, we seldom really have any particularly strong information on what this is. So we're leaving the defaults at root 10. But we are pointing out that some specific organ systems and toxic endpoints have been identified as of particular concern. And you may recall the discussions we had on that point when we were working on the SB 25 prioritization document back in 2001.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: And with that in mind, we point out that there are a number of types of toxicity which we basically regard as red flags and that there may be a justification in cases where these are seen, depending on what data we have or might be looking at. In many, many of these case we were thinking it appropriate to increase the value of UFH-d because of the specific sensitivity in infants and children to these endpoints.

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CHAIRPERSON FROINES: We don't have anything that helps us on the issue of in utero or early life exposure and then impact throughout life, which I think is --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We consider that as a developmental impact, yes.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: And we would consider -- if we had data showing that, we would definitely increase that -- you'd use the data or you'd increase the uncertainty factor.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We'd either use the data or -- yes. If we had the data, we'd use it, you know, as the endpoint if we didn't have the data. But we had grounds for suspecting the effect was there. Then we would increase the uncertainty accordingly.

And there's an additional point here. The next thing I want to talk about actually does have some bearing on that, in that we are proposing in certain cases to use a data deficiency uncertainty factor. This is something which U.S. EPA has used for some time. We didn't use it before, but we think that particularly with the more clearly defined criteria which U.S. EPA has developed and which we've attempted to enumerate in the document, that

it would be useful in specific cases.

A particular concern is where we are lacking developmental toxicity studies. If we have enough data to suggest that there's something specific going on in the developmental toxicity area, we would address that by looking at the at the UFH-d and the UFA-D. In other words if we have data suggesting something going on, we'd use it, and it would appear in that area or either as an uncertainty factor or as a model. But if it's a case of we just don't have any data but we nevertheless have our suspicions, then we would fall back on the use of the data deficiency uncertainty factor.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We --

PANEL MEMBER BYUS: Again, that's the heart -- that's the -- the data deficiency one is the most difficult of your uncertainty factors for me. I mean I do think it's okay, and you have defined it, although --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, it is --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It's a release valve really is what it is.

PANEL MEMBER BYUS: Yeah, I know, I know.

And is it the only place it's defined is on page

44? Or have I just missed it?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: No, I think you're right. We have a very small paragraph on it. It's really a --

PANEL MEMBER BYUS: But I'm not sure -- as I keep reading it over and over again, it gradually sinks in. But --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, it is --

PANEL MEMBER BYUS: But it's the softest statement there. And I -- everything else, all the uncertainty, the factors in my opinion are very nicely backed up, models beautifully done, very nicely done. Difficult to argue with, except for this one.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: This one is just --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Page 64 on my printed copy, Section 449, uncertainty associated with deficiencies in the overall database, is where we have it. And what we did at the last meeting, we said we will go back and look at how EPA in their 2002 document describes it. So we literally put that description in. And it essentially gives the risk assessor a way to look at the totality of the database, what is there, what is not there, and allows you -- if you

really think there's just not enough data for us to be comfortable that that is a health protective value, it allows you to add in another uncertainty factor. So that's really what we're getting at.

I don't honestly know how often we will end up using it.

PANEL MEMBER BYUS: It's that one sentence in the middle there. It says, "In addition to identifying toxicity information that is lacking, review of existing data may also suggest that a lower reference value might result if additional data were available."

Now, what you mean exactly by that sentence is my -- that's what I don't -- if you gave me an example --

CHAIRPERSON FROINES: Where are you?

PANEL MEMBER BYUS: I'm on page 64.

CHAIRPERSON FROINES: So am I.

PANEL MEMBER BYUS: Okay. It's the --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It's the quote from the U.S. EPA document?

Right, it's up -- 449

CHAIRPERSON FROINES: Oh, yeah, oh, yeah. I got it.

PANEL MEMBER BYUS: It's that one sentence. And it just -- if you gave me an example.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: You know, I think -- it's hard to give examples, and let me tell you why.

PANEL MEMBER BYUS: I know. And that's why it's --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I mean every single chemical that we run across -- you know, we're not dealing generally with pesticides or drugs where there's a lot more toxicity information. We're frequently dealing with something that, you know, no one has really done full blown set of toxicity testing on. So every situation that we end up looking at the database is unique. And sometimes you will look at those data, or if you have -- for example, you're looking at a chemical that is structurally related to something that you know has a lot more toxicity than is indicated by the very minuscule database that you have working on. There is an example where --

PANEL MEMBER BYUS: There's a good example.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- you might add in another database uncertainty factor.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Or if you know that there's a metabolite about which you have some suspicions.

PANEL MEMBER BYUS: If you could just put that

sentence --

PANEL MEMBER BLANC: That's an example of where there's a data deficiency. What is an example of something where the existing data suggests that there's a data deficiency?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, the existing data would be in this case on the analog chemical, on an analogous chemical that's structurally related. So, you know, if you're looking at everything possible about that chemical or class of compounds that you know about.

PANEL MEMBER BLANC: Well, how about an example where there was an effect compared to controls but the study size was so small that it was difficult to tease out whether it was due to chance or not. And then you suspect that if you had a larger study -- I mean wouldn't that be an example where the data show the need for more data?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. A good example of that might be, for instance, a developmental study which only had one dose which was fairly high. So you knew there was an effect, but you didn't know what the dose response was. That would be an example.

PANEL MEMBER BYUS: But you did a nice job of examples all through here, really. And that made it to me

when I read it very clear. That's the -- so if you just gave me one -- put one example -- I believe you, I just -- you need it. It's just too soft.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

PANEL MEMBER BLANC: But is there -- you haven't --

PANEL MEMBER BYUS: I wanted to say something.

You don't want it to appear that it's arbitrary. That's what I'm trying to tell you. And I know you're not doing it in an arbitrary manner.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, we get it. I understand.

PANEL MEMBER BLANC: I think another potential source of confusion could be a situation where you end up even -- you have human toxicokinetic and toxicodynamic data. And because of the multiplication factors you end up with a greater uncertainty multiplication than you would had you only had animal data. Is that mathematically possible? Does the maximum uncertainty that you could get with your factors for human data ever multiply out to more than its -- it's 3 times 10 --

PANEL MEMBER BYUS: You said 3,000 was your max, right?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: I don't think we've ever had that problem. I mean if it's done in humans, then your whole intraspecies extrapolation you don't need to worry about.

PANEL MEMBER BLANC: So mathematically it can't come out to be --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I don't think it would ever come out that way.

PANEL MEMBER BLANC: I mean I think you should think of if there's a nice way of saying that in a sentence, you know, or -- because the tables are separate, aren't they, for -- there's no table that includes -- because it would be very bulky. But, you know, the human extrapolation one is one table and the animal one is another table. And then the uncertainty factors when you don't have toxicokinetic data is another table, right?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It's all on Table 441 on page 45. UFL, UFA, UFA-k, A-d, H-k, H-d, and S. But I think it would be hard to answer your question just looking at this table. You'd really need examples. But, you know, having dealt with an awful lot of reference exposure level development, we've never had the issue that you're talking about.

CHAIRPERSON FROINES: I think this issue that Craig's raising is really important. And it is potentially a huge issue, because we're always dealing

with too little data.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, I think too it's safe to point out that if we ever used the database deficiency factor, we would justify it within the individual chemical summary. And so it would be out there, "Why did you guys use this?" And people would be able to say, "You shouldn't because of this reason" or "here's some data you overlooked." So, you know, it definitely would not be done just by us and stick it out there.

PANEL MEMBER BYUS: Arbitrary.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah. I think one of the --

PANEL MEMBER BYUS: So I mean if you want to use the word -- I would use the word, not done in an arbitrary manner and highly justified, for example, just as a -- because, again, it's just -- you gave nice examples. You really put in a lot of effort into trying to anchor every statement with some example. And that came across as a real strength to me when I read the document, because it kept anchoring it back to why, why, why and an example. And then I got to this one, it was like I still -- you know.

PANEL MEMBER BLANC: But am I missing something, that if we come back to this table on page 46, isn't the maximum 30 for the intraspecies uncertainty and the maximum is only 6 for the interspecies?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: No, these are defaults, not maximum, by the way. But just -- you know, these are default values which we recommend in the absence of more specific information to the contrary.

PANEL MEMBER BLANC: Right. But these defaults, the possible default would only be 6 for interspecies but it could be 30 for the intraspecies.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: If you're just looking at the default?

PANEL MEMBER BLANC: Yeah.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: And you're comparing the toxicokinetic UFs for interspecies versus intraspecies.

PANEL MEMBER BLANC: Right.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right.

PANEL MEMBER BLANC: Is there some other step I'm forgetting? Let's say --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: No.

PANEL MEMBER BLANC: Let's say you had the animal toxicologic data and you needed to put in a default uncertainty factor to --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: But if you were using the uncertainty factor defaults for both the kinetic and the dynamic components, then you have an overall UFA of 10.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: And an overall UFH could be higher.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The overall UFH could be 30 by, you know, using the defaults.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: But they would be layered one on top of the other if you started with animal data.

CHAIRPERSON FROINES: I'm missing that. Could you explain that.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: If you were starting with an animal experiment, you would take your NOEL or benchmark, you would divide it by square root of 10 for the toxicokinetic component of interspecies extrapolation. You would divide it by a further square root of 10 for the toxicodynamic component of that. In other words, an overall division by 10 for the interspecies extrapolation. You would then

take the result of that calculation and divide it by a factor of most often 10 to represent the intraspecies variability in the human species. And the further factor of 3 for the toxicodynamic. In other words, the factor -- the division factor overall to deal with the diversity within the human species is, by default, 30.

PANEL MEMBER BLANC: Plus times 2 if there was --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, I see -- okay, Paul, I -- yeah, okay, I see the confusion.

In the table, within a single box, we're saying these are possible defaults, that you don't multiply those together.

PANEL MEMBER BLANC: Oh, they're the most it could be.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right, exactly. And that --

PANEL MEMBER BLANC: Right, gotcha.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: The most it could be default. If there were other things going on, you might actually have more -- we do have a statement in there regarding that, but -- yeah, you don't run down and multiply them all together in one box and compare one box to the other.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: It's the value chosen within the box in each case.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. I think maybe we need to make this table a little clearer, how we were using it.

CHAIRPERSON FROINES: You need to not have it at the table. You need to have it as a dynamic process in which you actually show going from step 1 to step 2 to step 3.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

PANEL MEMBER BLANC: No, I think you could do it with just another column which says "Maximum Possible Uncertainty."

PANEL MEMBER GLANTZ: Well, no, the maximum possible is 10 for each one of these. I think it's just a question of labeling it better.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, just labeling it. Okay.

CHAIRPERSON FROINES: The fact that --

PANEL MEMBER GLANTZ: Maybe you could change the title to say, you know, value -- I mean this isn't the best language, but to say, you know, value -- possible values to be selected from or something like that. That's not grammatically wonderful, but to make it clear that

it's one of -- one in each box.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We'll label --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: The other thing you do is put in more lines.

PANEL MEMBER BLANC: Sub-lines, little dotted lines?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, little lines. Okay.

CHAIRPERSON FROINES: I'm still -- and I'll let this go right away. But I'm still uncomfortable with this square root of 10 business, because it's wholly dependent on the fact that you're developing toxicokinetic and toxicodynamic models that tests whether or not this square root of 10 is adequate. I don't know if the square -- dividing -- well I guess it's based on the fact that you believe that you can develop clear pictures of those parameters over time, huh?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, I think -- really what we're doing is saying that the traditional safety factor of 10 or uncertainty factor of 10 is a half log for kinetics and a half log for dynamics. There are some studies out there that have

looked at using the traditional defaults of 10 for interspecies and intraspecies and seeing are those really adequate. And in general for many chemicals, they are. But when you start digging, looking at the distributions of kinetic factors in humans, you start to realize that, well, there are a lot of chemicals they're not. So that's really where the root 10 comes from, is just thinking about it as these two separate contributions.

CHAIRPERSON FROINES: You know, we had a whole day-long meeting on this topic some years ago.

PANEL MEMBER BLANC: I think, by the way...

PANEL MEMBER GLANTZ: He's saying give the stenographer --

CHAIRPERSON FROINES: I understand what he's saying.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Should we -- I think we're pretty close to finish, because --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, there's not very much left of this part of the thing.

--o0o--

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The LOAEL-to-NOAEL uncertainty factor is something you'll recognize from the previous version of

the guidelines. And what we're saying is that it's -- actually we changed this a little bit from the public review draft, and we've essentially gone back more to what we had with the original proposal. The original proposal was for the cute RELs that we had a table of effect severity and that we would use a UFL out of 6 or 10, depending on whether it counted as a severe or a mild effect.

We had attempted to apply that this time around with the chronic RELs as well. But the conclusion when we've done that and we looked at it and we looked at the comments we received, we essentially concluded that that severity basis really doesn't work very well for chronic LOAEL to NOAEL extrapolations.

So what we are basically saying is that we would most usually be using a tenfold value for the -- for a LOAEL-to-NOAEL uncertainty factor for chronic situations. But we do -- we are prepared to consider some other indications, which would be similar to what we had in the previous chronic guidelines, where you have a low incidence LOAEL or a weak statistical significance LOAEL. We think about, you know, do we have a mild effect thing in there. We come to the conclusion that very few things which are actually chronic toxic effects would be considered mild in that sense. So that's why we really

backed away from that.

But the other thing which is different in this version of the guidelines from what we did previously is we hope that we are relatively seldom going to be using this. Because when we have reasonable data, even if there isn't an actual NOEL identified in the date, we can generally run a benchmark concentration analysis, which does give us a firm point of departure, which has the same properties as a NOEL. So in that case, we would not use the UFL. We would use the point of departure calculated from the data. And we would use the same uncertainty factors as we'd apply to the NOELs for most data.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So just a reminder that that intermediate factor of 6 was based on a derivation from acute studies and mild effects. So that's where the intermediate factor of 6 came from in our last go-around with the document. So we're pulling it forward, and we were going to try to use it also in the repeated 8 hour or chronic. But it ends up falling apart when you think about it, and this was pointed out to us by some comments.

PANEL MEMBER FRIEDMAN: So I'm still not clear why you picked 6.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Because it was actually the 95th percent of the

distribution for subset of chemicals for acute low LOAEL to NOAEL ratios. So that's why we had picked 6 --

PANEL MEMBER FRIEDMAN: And That was just for --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- in the '99 guidelines.

PANEL MEMBER FRIEDMAN: That was just for mild effects?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It was for mild effects and it was acute exposures. So, you know, when you start trying to think about, well, we're actually trying to protect people from essentially almost continuous exposures, it starts to fall apart trying to apply that in a chronic or repeated exposure scenario. So that's why we're ditching that now.

PANEL MEMBER GLANTZ: So you're just going to stay with the 10?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: For the chronic, unless we have -- you know, unless you can look at the dose response curve or have other information that you're actually not very far from the NOAEL, you're considerably less 10x, because its steep dose response curve might be one thing to look at, you know.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: But having said that, it's less likely that

we would be using this factor in a situation where we had dose response information. Because if we have dose response information, unless there's something very objectionable about the quality of the data, the chances are that we could do a benchmark concentration analysis if we had that sort of information. So hopefully we would get away from this conundrum in that case.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Another thing which we have -- again, this is a variation on what we did previously. But for acute toxicants we have used a modified version of Haber's Law to provide a time concentration adjustment, where we need to take, for instance, a two-hour acute study and derive a one-hour REL or something like that.

We're continuing to use the modified Haber's Law approach. But we're recommending -- I mean in the cases where we don't have actual measured values of the exponent A -- which of course we do for quite a number of chemicals which are listed in one of the appendices. But where we don't have measured values for A, we're going to assume a default N of 3 now rather than what we previously assumed with 2. This is consistent with what U.S. EPA now does and also consistent with some more recent data on chemicals in general.

Further exceptions to this are that when we're talking about a sensory irritant response, we have evidence to show that in fact the time dependence of that is rather different. The sensory response reaches a plateau in a period of time something between a matter of seconds and minutes, and is then essentially constant at least over the sort of period of which we're interested for an acute REL of one hour.

And therefore we're not going to be using Haber's Law to adjust concentrations for sensory responses to irritants. We're going to just use the concentration dependence since that's the important dose metric in that specific case.

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AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I might add that the value the exponent 3 over 2 weights more heavily the concentration term than the time term. So it's actually a little more health protective to do it that way.

CHAIRPERSON FROINES: Andy, I think that you've come to a place where we should break, because your next slide, as I look at it, is on the reference levels for the specific --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. I was not going to talk about them

myself in detail. What I was going to do actually here was say, well, this is -- you know, this is the next step of the process.

And there are two things that we have to present to you: One is the new RELs. And staff who are responsible for those are available to present those to you.

And the other thing which I have for you, which you can consider now or at some other time, depending on what you want to do, is that we have received a number of comments. And I have I think sort of grouped and paraphrased the comments that we've received and our responses to them. So what I hope is a reasonably brief coverage of the areas of comments that we've received.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It's up to you. So it's up to you however.

CHAIRPERSON FROINES: Well, my question -- but you've made much more complex the issue of a ten-minute break. So --

PANEL MEMBER GLANTZ: Let's just take a ten-minute break.

CHAIRPERSON FROINES: So Let me just ask one question. When we come back, is that the appropriate time to ask Stan to give his views of the process that he went through, representing the Panel as the lead person, before

we go on to the RELs and the comments?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes, in fact it is. I mean my first slide in discussing the comments, among other things, essentially says we talked to Stan. So that would be a very --

CHAIRPERSON FROINES: So we'll come back and put Stan --

PANEL MEMBER BLANC: -- on the stand.

CHAIRPERSON FROINES: -- on the hot seat.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

CHAIRPERSON FROINES: And let's take a break.

(Thereupon a recess was taken.)

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Just one clarification. We do have slides on summarizing the comments received on just the TSD. I don't know if the Panel is interested in hearing those before Stan or not at all or after Stan.

CHAIRPERSON FROINES: You have commentary on --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- the comments received, just on the methods part. We have slides of those and our responses. But

you've all read the comments and responses. So I don't know that it's necessary to go over them.

CHAIRPERSON FROINES: I think it would be valuable. But I --

PANEL MEMBER GLANTZ: Yeah, I think I -- I mean I'll tell you -- I mean basically what I have to say is that I read through all of the stuff, made a lot of comments. There were a bunch of inconsistencies, some of which some of the other Panel members have pointed out. And had two meetings with Melanie and Andy. And I think -- and in the SRP revision they had I thought dealt with most of the things I had raised. That was on the previous draft.

Then when we met a few days ago, we went through the current SRP draft. I think most of the things were dealt with reasonably. I had some questions about how they dealt with some of the public comments. And we also had a big discussion about how they were going to discuss the strength of association, which is the thing that was handed out, which I was unhappy about.

And what you have is the result of sort of a compromise. And Paul Blanc just edited this and made it clearer.

So that -- I mean I think it would be better to just let them go through the response to comments.

Because I think that just looking at the slides, some of them are going to deal with my comments. Right?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

PANEL MEMBER GLANTZ: And they remember them better than I do at this point.

CHAIRPERSON FROINES: Can we talk about this and then go to the comments?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Oh, yeah.

CHAIRPERSON FROINES: And so in essence you've just given your presentation?

PANEL MEMBER GLANTZ: I have. I've given -- I think that what I would suggest we do is let them present the response to comments about the technical support document, and then stop and finish the discussion of that, and then go on and talk about the individual RELs, which is the application of the technical support document. I mean that would be my suggestion.

But I think that what their report is going to have, the main thrust of my more significant comments to them. And as I said, there were a lot of inconsistencies in the document that have been fixed.

I think overall it's a good piece of work.

And the other thing, which hasn't actually -- I

haven't talked to them since we met a few days ago. But there were a few issues in the response to comments from the public commenters that I also thought needed to be better addressed, which I hope you're going to talk about.

No?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, no, I can't. I haven't stickied.

PANEL MEMBER GLANTZ: You have your stickies. Okay.

Well, I have my notes from that if we need to.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: So I'll just run through the public comments received at this point.

PANEL MEMBER GLANTZ: Yeah.

CHAIRPERSON FROINES: No, no, no. I thought we were going to talk about this issue here.

PANEL MEMBER GLANTZ: Okay. If you want to do that, we can do that.

CHAIRPERSON FROINES: And then we can go to the comments, because they are separate.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. I think Peter handed everyone this revised paragraph on strength of association.

As Stan mentioned, we went back and forth on it. The earlier paragraph had explicit cutoffs for weak versus

strong association that really aren't found in a textbook anywhere. They're sort of the way people thought about it for a while.

Also our original paragraph really focused more on the size or the magnitude of the effect estimate or relative risk rather than other things that influenced the strength of association, such as the statistical significance and the study design and how well it dealt with confounding and so forth.

So that reflects -- this new paragraph reflects that discussion. And then Dr. Blanc has clarified it further.

PANEL MEMBER GLANTZ: I mean basically the thing that I was hot and bothered about was they had this thing about a large effect being a factor of 2. And I don't think there's anything magical about that. And there's examples of studies that have found big effects that were flawed. And there are also lots of examples of things where you get a relative risk well below 2 where you have very strong evidence that it's real. And so I wanted that clarified, because I just think this 2 number has just been pulled out of the air basically. Although Paul explained to me there is some litigation context in which it's important.

But to me what I'm -- I don't even like the term

"strength of association," although I think we're kind of stuck with that because people are used to talking about it. But I would almost call it like "quality of the association" or "convincingness of the association." And for that I think you need to look at the quality of the study design, as we said, adjustment for confounding, whether or not the result is statistically significant. And to me the magnitude of the effect, which is detected as less important -- I mean in fact it's harder to defect a small effect than a big effect. So that's kind of built in to whether or not it reaches statistical significance in my view.

So this was the result of a lot of ping-pong Emails back and forth where I was suggesting -- they suggested one thing, I rewrote it, they sent it back, and we kind of converged. And I think the net result of when you write a paragraph by Email ping-pong is sometimes it gets a little disjointed.

Paul made a few editorial suggestions, which I think further clarify the points that I just made, which Melanie has. I mean if you want, we can go through them. But I think they're more editorial in nature and clarifying.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So this would replace the paragraph on page 30 at

the bottom of the page under "Strength of Association."

CHAIRPERSON FROINES: I'm sorry. Peter asked me a question. I didn't hear what you said. Sorry.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: This would replace the paragraph on page 30 at the bottom of the page.

CHAIRPERSON FROINES: The first thing I would say is you should -- Ken Rothman and Sander wrote another causality paper that was published in the American Journal of Public Health that's only about two years old. And I will send you the paper. And it is basically their most recent consideration of the issues of causality.

PANEL MEMBER FRIEDMAN: Would you send that to all of us, please.

CHAIRPERSON FROINES: Oh, absolutely. That's what I -- yeah.

And my only question is the -- I don't know what you mean by the level of statistical significance. Because we all know that there are people who, if something's greater than .05 at 95 percent -- there are people who make decisions in very rigid ways. And what I think is we have to be very careful. And Toby Paige from Brown University wrote a statistical paper some time ago where he looked at different implications of different statistical approaches defining causality. And he thought

that from a public health point of view one needed to have a broader perspective.

PANEL MEMBER GLANTZ: Well, no, and I'm not -- I certainly agree with that. What I was -- the way I interpreted that is that if you have a very highly significant result, okay, and a well designed study, you can have a lot of -- I mean a lot of confidence in it. But this did not mean to imply that .05 is the magic number and that, you know, .050001 is no effect and .049999 is. But I think -- you know, when I'm looking at a study that's estimating a risk, if you have a very small P value associated with that, that means you can have a lot of confidence that it's not a chance finding. That doesn't mean that if you -- that there's some magical cutoff. And that you could have -- if you had -- if you had an effect which was very severe, you know, it may be that you'd have a P value of .1 and say, "Well, I don't even want to take a 10 percent chance of this happening."

I mean maybe rather than saying statistical significance, we could say -- and this is one of changes that Paul was suggesting -- is to say the level of Type 1 error.

CHAIRPERSON FROINES: That's better.

PANEL MEMBER GLANTZ: Or the level of alpha error, which is what he's saying. Or the risk of a false

positive.

CHAIRPERSON FROINES: My concern is that there's a whole world of people out there who are very dismissive if you don't reach a certain level.

PANEL MEMBER GLANTZ: Yes.

CHAIRPERSON FROINES: And they can take data for which look like they're a clear risk that don't make it to that level and they dismiss the study.

PANEL MEMBER GLANTZ: No, I mean I totally agree with that.

PANEL MEMBER FRIEDMAN: Yeah, they say there's no effect -- when like it's 1.2 but the lower confidence bond is like .95, well, then it's no effect.

PANEL MEMBER GLANTZ: Yeah. No, I totally agree with that. In fact, when I teach this stuff, I now have -- and in this little book I wrote, Primer of Biostatistics, that goes with Gary's epidemiology book -- I actually went back and found Fisher's original paper where he suggested .05.

(Laughter.)

PANEL MEMBER GLANTZ: And you read it and it said, "Well I thought about this and 1 percent seemed too small and 10 percent seemed to big, so why don't we use 5 percent." I mean it basically says that. It just says, "I thought this was a reasonable number."

I mean the point I make to the students is that it's not -- .05 is not like Planck's constant or the speed of light or pi, you know. It's just the numbers one guy thought was a reasonable number. So we're all in agreement about that.

The way I interpret --

CHAIRPERSON FROINES: I just think that the way this is phrased though is that --

PANEL MEMBER GLANTZ: Well, no, we can fix that.

CHAIRPERSON FROINES: -- people can interpret -- people have biases. We all do. And people will interpret it to fit their bias.

PANEL MEMBER GLANTZ: Right. I mean the way that what I tell people -- which is I think what they mean here, but we can clarify this -- is that the P value is the measure of the certainty you have in the conclusion that you're drawing, and that that should be a guide in making a decision where you consider the costs of false positive or false negative solutions.

And it's not -- .05 is not, you know, as Gary said, the dividing line between effects and no effects. But we can clean this up.

This is certainly all in the spirit of what I was trying to accomplish in asking that this one paragraph be rewritten.

CHAIRPERSON FROINES: It's great work, Stan. If they had walked in here with a 2 as -- that would have caused the reaction.

PANEL MEMBER GLANTZ: Well, it already did. I pre-reacted for the Panel.

(Laughter.)

PANEL MEMBER BLANC: Stan, I don't know if this a question for you or for them. But in the section that precedes that, where a list of the methodologic issues -- of selective methodologic issues --

PANEL MEMBER GLANTZ: What page is that on?

PANEL MEMBER BLANC: The same page.

PANEL MEMBER GLANTZ: Well, what page is it on?

PANEL MEMBER BLANC: Thirty. "Methodologic issues that are considered in a review of the epidemiologic literature include" -- and you have, you know, four obvious examples.

I wonder if, with Stan's help, you might not want to put a few more in there that would help you potentially in terms of other outside commentary you might get, because you --

CHAIRPERSON FROINES: Where are you, Paul?

PANEL MEMBER BLANC: It's the --

PANEL MEMBER GLANTZ: Page 30 on the top.

PANEL MEMBER BLANC: The top of the page.

You know, for example, I'm sure that in looking at studies which have negative findings which you take with a grain of salt that are based on occupational cohorts, which is what you're forced to use, you take into account survivor effects and the healthy worker effect. And although you talk about selection bias, you don't say the health -- you know, in particular, the healthy worker effect, you don't talk about survivor bias and you don't talk about over-adjustment for factors which are intermediate in the causal pathway. And I think that those are some things that you're doing all the time. And since you're listing things here, I think --

PANEL MEMBER GLANTZ: Yeah, I think that's a good idea.

CHAIRPERSON FROINES: I think that exposure misclassification is a crucial issue.

PANEL MEMBER GLANTZ: Yeah, I agree with that too.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, that was number 4.

PANEL MEMBER BLANC: What do you mean by bias?

PANEL MEMBER GLANTZ: Well, you know, actually as I was sitting here listening to Paul, I was thinking we should also have an exposure misclassification. That's really different than exposure assessment, that's

different than bias in ascertaining --

PANEL MEMBER BLANC: Because then bias is towards the null, isn't it?

PANEL MEMBER GLANTZ: Right. And bias and ascertaining exposure could go either way.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right.

PANEL MEMBER FRIEDMAN: And there can be bias in ascertaining the outcome too. I mean do we want them to have to --

PANEL MEMBER BLANC: I think they should just have enough things there that -- what I think they've done is selected all the things that would be the -- sort of on the side of saying, "I disbelieve this positive study." But there's not very much here that is -- some of the stuff that's very relevant to discounting negative studies isn't as much here, except for the sample size, I suppose. If you know what I mean.

PANEL MEMBER GLANTZ: Yeah, I think those are good things to have.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, I think we can add -- the over-correction issue is a huge one. And we can have healthy worker effect in there, you know. It is not meant to be exhaustive, and we tried to be --

PANEL MEMBER BLANC: No, I know. And in fact you need to put --

PANEL MEMBER GLANTZ: Melanie, I agree and I, you know --

PANEL MEMBER BLANC: And I would put selective methodologic issues just to underscore that.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay, sure.

PANEL MEMBER BLANC: But I would still loose it up a little bit if you -- you know, it's not the be-all and end-all. But if you have the energy and --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Sure.

PANEL MEMBER BLANC: Because I think it undersells what you actually do.

CHAIRPERSON FROINES: Yeah, I think -- I actually think these issues are extremely important for the fact that they get misused so often. I mean it's not -- this is not a neutral issue.

PANEL MEMBER GLANTZ: Yeah, that's true, because all of these items aren't reasons to discount a significant finding -- a statistically significant finding. I think that the -- that it would be good to have other things where, you know, the presence of these problems would make you discount a negative finding.

CHAIRPERSON FROINES: Well, I'm reviewing a paper right now in which they have a statistically significant finding, and then in the discussion they actually show all the reasons why it may not be a causal relationship. I mean it's going as far as they can --

PANEL MEMBER GLANTZ: -- these secondhand smoke studies that come up positive, they do that. It's like, "Well, we found this result but we don't believe it." Because we're idiots. Anyway --

(Laughter.)

CHAIRPERSON FROINES: So I think we're set on this and that we should move ahead with Andy.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, I'll --

PANEL MEMBER GLANTZ: Well, I just have to say I'm glad that it was good that I made an issue of this, because I actually had given them a hard time about this. And they forgot to address it after the first meeting. See, it was --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Which sat really well with Stan, let me tell you.

(Laughter.)

CHAIRPERSON FROINES: But the issue of the -- there's been so much debate about this value of 2 as, you

know, the gold standard, that it's good that you dealt with it.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, we've had our discussion on the comments from the Panel, so I'll move on to the public comments here.

First comment, which we received from several people, was that the increase of the UFH-k was unjustified or that there was a sufficient safety margin provided by overlap of other uncertainty factors.

PANEL MEMBER FRIEDMAN: Could you speak a little louder.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Sorry. I'll try and get closer to the microphone here.

Well, we disagree with these opinions. And we provided what we think is a fairly detailed refutation based on not only our own work but quite an extensive body of recent studies from the scientific literature which we think supports our proposal.

So that was the first comment.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The second comment was about the same topic, but in the other direction. The suggestion was

instead of adjusting default values, that we should actually include a specific tenfold uncertainty factor for children's special sensitivities. These obviously would be larger than what we proposed.

We considered the option of having a special sensitivity factor of some size for children, but decided that in fact modifying the existing default uncertainty factors was easier to evaluate and to defend. And we also note that OEHHA's actual proposal in the document you have is similar in effect to the way U.S. EPA handles the process of determining the need for and value of an FQPA factor which they determine on a case-by-case basis.

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CHAIRPERSON FROINES: That may not be a -- never mind.

The fact that EPA does something these days doesn't necessarily guaranty that we would agree with it.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: No. Well, I think we're merely observing in this particular case we're not so far apart as we sometimes are.

The third class of comments were the concerns which I think we've already talked about a little bit, about how the LOAELs and NOAEL uncertainty factor was defined and used. And as I said earlier, we have in fact

addressed this by confining the acute -- the mild and severe consideration to the acute, which is where it originally came from, and using basically for the most part tenfold for chronic but with the possibility of other factors where we think that would be appropriate.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: A fourth comment. We had some suggestions about the 8-hour REL. And in particular, as I mentioned, that we should -- in addition to developing child protective 8-hour RELs, that we should also develop 8-hour RELs suitable for adult-only exposed populations.

We agree in principle this would be a reasonable thing to do in certain cases and that we are saying that we will consider doing that in the future.

There's a couple of points there. Firstly, that we'll do that in specific cases rather than just across the board. And the other clarification is that in fact how these different versions of the 8-hour REL are going to be used will be covered in the forthcoming revision of the exposure assessment guidelines.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We received comments where the comparisons were made between the values --

CHAIRPERSON FROINES: Are you comfortable with -- I don't know whether -- are you comfortable with the 8-hour REL?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, it depends on -- you know, I mean -- the way it would be used is for facilities that only emit eight hours a day. They're only open eight hours a day, and that's when they emit.

In the past what we did was take that and average it out over 24 hours and apply the chronic REL. And so, you know, we were concerned that we're not really taking into account the effect of peak exposures and then zero exposure. So that is why we thought it would be better if we had an 8-hour REL useful for evaluating those kinds of situations.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: There are some -- well, there are many cases where the 8-hour REL will be the same as the chronic REL distributed over an 8-hour or a 24-hour period. But there are some cases where it won't be for specific reasons to do with the way the chemical toxicity goes and what major defects --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: -- and kinetics.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: -- and the kinetics and so on.

PANEL MEMBER BLANC: Then do you provide -- in your response, even if not in the document, wouldn't it make sense to provide an example of that to be appropriate critique? I mean, for example, a work site that's emitting carbon monoxide, I can really see the rationale for wanting to have an 8-hour REL as opposed to averaging that out over 24 hours, which --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Most of the comments that we received in relation to this generic topic actually have roots in the manganese assessment. So --

PANEL MEMBER BLANC: I don't care what they have roots in. But --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Yeah, so I think what I'm saying is that you may see some compound-specific responses on that topic when you get the manganese responses, which we're -- but unfortunately we haven't got those because we're not done with the assessment yet.

PANEL MEMBER BYUS: Yeah, I think you did a good job describing the 8-hour, the rationale for it, providing an example. I liked it.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: As I say, the complexities come in later

when you get the exposure assessment.

PANEL MEMBER BYUS: Maybe I read some of those. But I think it is of value to do it, potentially; that you could really miss something if you didn't. So when you can, it's good.

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CHAIRPERSON FROINES: Does this mean you're going to be doing permissible exposure limits for CalOSHA now?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, I don't think we're allowed to answer that question.

(Laughter.)

CHAIRPERSON FROINES: Well, but do you understand the implication of having an 8-hour REL for adults is precisely that it's -- you're setting a standard. What you're saying to CalOSHA, this should be your approach. So it's not trivial. But it's really important because of the problems of standard setting in general.

Are we going to hear that little George Alexeeff comment?

OEHHA DEPUTY DIRECTOR ALEXEEFF: (Shakes head.)

CHAIRPERSON FROINES: No.

(Laughter.)

CHAIRPERSON FROINES: Let's move on.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Yes, the next one was that some people presented comparisons between proposed RELs and measured or calculated concentrations of the chemical in ambient air, showing that some RELs approach existing concentrations.

And our response is we note that these comparisons may be of interest to risk managers dealing with emissions or ambient levels, but they're not part of the consideration that goes into the determination of a REL.

PANEL MEMBER BLANC: Yeah. Was that the best response you could make to that? I mean I think that's part of the response. Isn't the inherent critique when someone says your level's close to what the ambient levels are, then what they're not saying is then why don't we see the health effects that you're talking about generally in the population?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: I think we also say, firstly, that the REL is a level of which we're reasonably confident that health effects will not be observed. And, secondly, that if in those cases where obviously ambient levels approach levels that might be of concern, then one of the things that we would be looking for is to see whether there are studies of health effects from that chemical at those levels.

Now, one of the big problems is of course that people say, "Oh, well, you're not seeing health effects at this ambient level." But many of the times that assertion is essentially based on hearsay rather than actual studies anyway. So, you know, nobody really knows whether there's an effect, because they haven't looked for a lot of these things.

But in the cases where they have looked and where there's a usable study, then that would have been part of the database which goes -- you know, which goes into the consideration of what the RELs would be.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I think the other issue is, you know, when people say that to me, I always think of PM and ozone. Well, if we set the standards at the levels that we could achieve in terms of a pollution, then, you know, we'd never have any health protection, we'd never be cranking them down. So to me looking at what is it out there and saying, "Oh, well, your number is lower than what is out there," it's really a red herring. It's a "so what?"

PANEL MEMBER GLANTZ: I think that what they -- I mean I agree with the way that they presented it.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We could strengthen the response to that a little bit.

PANEL MEMBER BLANC: That was my point, is I think you could say, perhaps not as explicitly as you just have, but you could elucidate those points a little more --

PANEL MEMBER GLANTZ: Well, what it actually says in the response is pretty much what Melanie just said. More -- I mean it's pretty strongly worded actually, and I think it's correct. I mean the point is that what we're setting here are levels that we think will be health protective, not talking about what's in the air right now. These are -- you know, could very well be goals.

So I think it's stated pretty clearly already. I mean you could look at it -- if you want to suggest there's specific rewording, you can. But I think if you read what's actually in the document, it's pretty strong.

CHAIRPERSON FROINES: It also is -- I mean what we've learned in the last ten years with respect to particulate matter is that we now know that there are multiple endpoints that we had not known in the past and PM is beginning to look like ETS in terms of the number of endpoints and that they're occurring at levels that are not -- that are ambient levels and that there is in fact adverse health effects -- quite significant adverse health effects going on precisely at levels that would be -- which we regulate. So it says that if -- we may not

be -- one has to assume that as you learn more, you may find more and therefore your values are -- that's part of a dynamic process.

PANEL MEMBER GLANTZ: Right. But even given that, that's really disconnected from what levels happen to be out there in the air right now.

CHAIRPERSON FROINES: Yeah. This is a silica problem. This is the silica problem.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Okay. Next comment -- we received comments from a couple of interested parties basically saying that they wanted us to include a risk assessment on non-cancer effects of diesel exhaust along with the other sample RELs.

And our response to that is that we're aware that this is a big issue and we are in fact working on it. But we've got -- you know, it wasn't going to fit within what we're doing here, but it is something which we're currently looking at.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Another comment which we received --

CHAIRPERSON FROINES: You did say -- what did you say? Because obviously for me this is a crucial --

PANEL MEMBER GLANTZ: They said they're working on that.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We're working on the non-cancer risk assessment for diesel exhaust.

PANEL MEMBER GLANTZ: It's just not in this document.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: It wouldn't fit physically or temporally.

CHAIRPERSON FROINES: I'm glad you used the word "diesel exhaust," because in my view we erred in some respects when we adopted what -- when we did what we did for diesel particulate, which oversimpli -- all our data suggest that the vapor phase co-pollutants are very important.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We received a number of comments, both for and against, or a mention of the general principle, which has been in place for awhile, that a cumulative uncertainty factor of 3,000 should be regarded as practical upper limit.

And our response to these is basically that we tend to agree with the interpretation that has come out of U.S. EPA's guidelines. It's not that we're saying this is

a hard limit of 3,000 which we will never exceed. We're saying that if an indication of the cumulative uncertainty factor exceeds 3,000, it probably indicates that there's a pretty poor supporting data. And that may be insufficient for derivation of a reasonably reliable health protective level. But that doesn't mean that we wouldn't be prepared to go with it in specific cases if we felt that was justified. But we see this essentially as a warning -- you know, this is a warning light on the dashboard, if it goes higher than 3,000, to ask ourselves whether the underlying data are of sufficient quality.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We have received a number of both supporting and dissenting comments on the UFD. I think we've probably covered that in discussion already. But our response is in line with what we said earlier. And we have in fact amended the wording of the technical support document a little bit to reflect some of those concerns to make it a little clearer. And we're obviously --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We will amend it further.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: We will amend further in response to the discussion today.

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OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I think this is the last one.

The comment was made that there are significant problems in developing RELs for chemicals, such as some of the metals, which are essential nutrients. And one commenter suggested that since there are homeostatic controls for such elements, the use of an interspecies toxicokinetic uncertainty factor was unnecessary.

We agree that there are certainly problems with developing health protective RELs for essential nutrients. But the details in fact did vary considerably between specific cases. And we didn't see any particular merit in the suggestion to reduce the UFA-K to 1 across all such cases. We thought that we would need to in fact look at the individual cases, try and decide what was most appropriate in each case.

So that's the end of my presentation.

CHAIRPERSON FROINES: What time is it?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: 11:35.

CHAIRPERSON FROINES: Shall we move ahead to the RELs?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Sure.

So I think we have staff coming forward to give presentations. We'll start with the --

PANEL MEMBER GLANTZ: Can I just say one thing before we do that?

CHAIRPERSON FROINES: Please. You should say as much as you want.

PANEL MEMBER GLANTZ: Oh, okay.

PANEL MEMBER BYUS: Well, let's not get carried away now.

(Laughter.)

PANEL MEMBER GLANTZ: Well, I was going to suggest -- when I came into today I was going to suggest that we adopt -- we approve this part of the document. But I think since we're meeting in less than a month or about a month, I'm going to assume that, except for the specific fairly minor tweaks that got discussed here, people are happy with what this part of the document says. Is that a fair...

Okay. And so I'll work with Melanie and Andy, and we'll get all these other things fixed up for next time and some findings written. So hopefully at the next meeting we can just approve the technical support document.

CHAIRPERSON FROINES: So you're actually proposing not to move today?

PANEL MEMBER GLANTZ: Well, if you -- or we could vote today, or alternatively since -- actually let me propose we do vote and just subject to, you know, the comments that we can pick up on in the transcript in cleaning things up. I guess why don't I move that we approve the technical support document. And then I'll work with the staff to get these corrections done, and we can then run them by the Chair.

Are people -- would you rather do that?

PANEL MEMBER BLANC: I think what I would suggest as a middle ground is that we make it clear that we are quite supportive of the technical document to the extent that it certainly should continue to be used as the basis for finalizing the individual substance-by-substance estimations that you're doing, and that we'll finalize -- give final approval -- we'll approve of a final text, you know, at the next meeting.

PANEL MEMBER GLANTZ: Okay.

PANEL MEMBER BLANC: Because I think that's what you're worried about. If we don't approve it, how can they continue to use this to go ahead and refine that.

PANEL MEMBER GLANTZ: Okay, that's fine. Why don't we do that. I mean we're not talking --

PANEL MEMBER BYUS: I think that, you know, as we discuss these chemicals, it will even make our --

theoretically the value of this document, it will even be greater. And maybe we will say something different or something even stronger than we might now. So I mean I think you are right. I would agree with you, Paul.

PANEL MEMBER GLANTZ: Okay. Well, so in the meantime I'll work with them to take care of everything that's identified; and with the idea that when we come back to the next meeting, it will be approved. I don't see any great huge controversial issues outstanding at this point.

CHAIRPERSON FROINES: Now, the issues I think that need to be worked on, it's interesting, are -- I think are minor with respect to what needs to be done. But they do reflect major issues, so that there -- it's sort of --

PANEL MEMBER GLANTZ: Right. But what I meant was I don't see any tremendous criticism of the document.

CHAIRPERSON FROINES: No. I think Paul said it.

PANEL MEMBER GLANTZ: These are all matters of clarification, nuance, making the presentation better. And then we'll draft some findings that we'll circulate before the meeting.

CHAIRPERSON FROINES: I think Paul said it. I don't --

PANEL MEMBER GLANTZ: Okay. So there's no need

for a motion or anything.

CHAIRPERSON FROINES: I think Craig or Gary would have disagreed if they didn't share that view.

PANEL MEMBER GLANTZ: Okay. That's fine with me.

CHAIRPERSON FROINES: Okay. Unless Melanie has -- unless there's some time issue that you absolutely need a different approach.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: No, it's fine.

CHAIRPERSON FROINES: So just to -- so the Panel thinks this is a fine document that needs some minor tweaking and that we'll approve the final version next month. But in the interim, it does stand as a standard around which to approach the REL determination.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. We'll start the chemical by chemical with acetaldehyde first.

This is Dr. Karen Riveles, who is in Andy's group. And she will make the presentation on the acetaldehyde REL.

So first we'll present what we did. And then if you want to hear a summary of the comments, we'll do that.

CHAIRPERSON FROINES: I should just say that I think acetaldehyde is going to become a major issue in the future. As long as we keep using ethanol and biodiesel,

this issue is going to just keep growing, in my view. So you got a good one.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Thank you.

Just by way of overview on the first slide, I've indicated what the final calculations for the acute 8-hour and chronic REL are.

The acute REL is based on eye irritation in human volunteers, was determined to be 750 micrograms per meter cubed or 420 parts per billion.

And I'm going to go into more detail on each one of these in the next slides.

The 8-hour REL and the chronic REL are both based on an animal study in rats on nasal degeneration of olfactory epithelium. And the 8 hour was determined to be 270 micrograms per meter cubed, and the chronic to be 140 micrograms per meter cubed.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: The key study for the acute REL determination was by Silverman, et al., 1946. It used human volunteers, an average of 12 subjects of both sexes per dose group, for a 15-minute exposure of 0, 25, 50, or 200 parts per million.

Motion pictures were shown to occupy the subject's attention during the exposure.

And may I note, it was 1946.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: The results of this study were that the 200 ppm's resulted in responses of bloodshot eyes and reddened eyelids in all subjects.

The majority, in quotes, of subjects experienced some degree of eye irritation as 50 parts per million and several subjects did at 25 parts per million.

Therefore, the lowest observable adverse effect level for a severe effect was determined to be 50 ppm and for a mild effect to be 25 ppm. No NOAEL was determined for this study.

And while words like "majority" and "several" are vague, that was all that was provided in the results of the study. But the strength of the study is that it was done in humans.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: So to review our REL derivation. Again there was a total of 24 adult human volunteers. The exposure method was inhalation. The endpoint or critical effect that was looked at was eye irritation. And a LOAEL for a minor effect -- mild -- excuse me -- was 25 ppm, while a NOAEL was not observed.

The exposure duration was 15 minutes. And this was not time adjusted due to what was mentioned earlier about Haber's Law not applying to sensory irritation.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: A LOAEL uncertainty factor for a mild effect was applied of 6 due to the fact a NOAEL was not determined.

Since it was done in human volunteers, the interspecies factor was 1.

Once again, we've divided the intraspecies uncertainty factor into two components, with the toxicokinetic component being 1 because it occurred at the site of contact in mainly a localized effect.

Whereas the toxicodynamic uncertainty factor was 10 due to the potential asthma exacerbation in children.

PANEL MEMBER BLANC: Because it's an irritant? Because it's a water soluble irritant? Would that be the rationale?

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Yes.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: There are also data indicating that there are people who react with hypersensitive airways in the presence of acetaldehyde. So it's a little bit more than just assuming --

PANEL MEMBER BLANC: There is?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah.

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: There are four or five studies that look at human volunteer adults that inhaled aerosolized solutions of acetaldehyde and were measured for SEV values for asthma exacerbation. And it was found that asthmatics are particularly more sensitive to the effects of acetaldehyde. But no studies were done in children.

CHAIRPERSON FROINES: Are there studies looking at inflammatory processes?

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: There are a few studies looking at inflammation, but not in human volunteers.

I don't have any further information on that.

PANEL MEMBER FRIEDMAN: This is a very minor nitpick, but on an earlier slide when you talked about method of exposure being inhalation, since it was hitting the eyes directly it didn't involve inhaling and then getting there, say, through the blood stream. So I was wondering if a better term might be airborne or -- airborne or something like that or atmospheric or something like that rather than inhalation. Very minor point, but relevant to the eye irritation I think.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: Yeah, it is a little bit kind of a confusing term in that case.

CHAIRPERSON FROINES: Can I just say one thing.

If you take two molecules of acetaldehyde and you condense them chemically and you lose water in the process -- a molecule of water, you form an unsaturated -- and alpha-beta unsaturated aldehyde. And alpha-beta unsaturated aldehydes form irreversible inhibition of a wide range of proteins, and that can result in inflammatory processes because it affects signal transduction pathways. And alternately you have the potential for cytokines, what have you, coming out of being activated by genes. And that can result in inflammatory responses.

So there's a potential for the chemistry that goes on with acetaldehyde to have quite significant asthma effects theoretically. And that's why I asked the question then. And it's going to -- that's an issue in terms of the chronic issues as well. Because if you're breathing it on a daily basis 24 hours a day, that chemistry is going on.

Anyway, go ahead.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: So that leads to a cumulative uncertainty factor of 60. And

dividing the 25 ppm LOAEL for a mild effect divided by 60 is what gives us the 750 micrograms per meter cubed, or 420 parts per billion.

While there are many acute animal studies that I've mentioned in the REL summary, most are done at much higher doses. And then you have animal to human extrapolation issues to deal with. So although this study was limited, it was the best available study because it was done in humans.

PANEL MEMBER BLANC: So can we come back to this issue of acetaldehyde as an inducer of airway -- of bronchial constriction. So you're review of the data is that basically you could use it instead of a methacholine challenge if you wanted?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It wasn't nearly as sensitive as a methacholine challenge.

PANEL MEMBER BLANC: But it will invoke bronchial constriction in asthmatic and normal subjects and will differentiate between asthmatics and normal subjects?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I think that the asthmatic subjects were more sensitive and -- Karen, you can correct me -- put I also remember that the acetaldehyde itself increased the sensitivity to methacholine challenge.

PANEL MEMBER BLANC: Right. So I guess my question is, was it the problem that these studies delivered an aerosolized dose that prevented you from extrapolating to an airborne concentration?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

PANEL MEMBER BLANC: But couldn't you extrapolate based on the nebulizer delivery system as to what the parts per million equivalent would be or the milligrams per cubic meter concentration?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: They were -- if you tried -- and I'm not sure that it's actually a valid way to do it. These were very large, very high concentrations if you tried to make that extrapolation. So in terms of a looking at a more sensitive endpoint, we already had that in our in ocular irritation.

PANEL MEMBER BLANC: Okay. But the ocular -- I mean two things about your ocular study. One, is not so thrilled to be using a 1946 study in 2008 just on general principles. Secondly, because your main extrapolation then to childhood exposure is based on increased bronchial responsiveness in asthmatic children, if you thought that the benchmark exposure for causing bronchial constriction was far above what your endpoint concentrations were for

the eye irritation, it wouldn't actually make sense then to put in the uncertainty -- the sixfold uncertainty factor, would it?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, we did talk about that a little bit. And part of the issue is how do you extrapolate from the studies they did in terms of the aerosol.

And then the other issue is that we have previously identified asthma as a disease that differentially impacts kids. And we don't have really very good information on whether the concentrations to which you would be exposed in the ambient air are adequate to actually trigger bronchial reaction. We decided to go ahead and apply that uncertainty factor for toxicodynamics anyway.

So the point you're making is definitely it's an uncertainty. And, you know, it's a question we thought about but went ahead and applied it anyway.

PANEL MEMBER BLANC: And when you said that when you did the conversion from the nebulized concentration to some kind of airborne milligram per micrograms per cubic meter, what kinds of -- what kinds of parts per million were you coming up with, as opposed to 25 -- 25 parts per million was how much in micrograms per -- milligrams per cubic meter? I'm sorry.

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Forty-five.

PANEL MEMBER BLANC: Forty-five milligrams per cubic meter.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, my back of the envelope was about five grams per cubic meter if it was -- even if it's, you know, doable to take an aerosolized spritz and try to figure out what that would be in milligrams per cubic meter.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The big trouble this that extrapolation is that you don't know how the deposition is going to be working between a vapor phase exposure versus an aerosolized exposure. One suspects a lot of the aerosol would be depositing in the upper respiratory tract, for instance.

PANEL MEMBER BLANC: I don't -- I mean if De Vilbiss nebulizer gets pretty fine particles that get into the airway, that's why you use it for a test of bronchial constriction.

Who is the primary reviewer for this? I don't want to step on someone's toes.

PANEL MEMBER GLANTZ: You don't?

(Laughter.)

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF

MARTY: I believe -- according to my -- Dr. Froines was the lead on acetaldehyde.

CHAIRPERSON FROINES: I didn't remember that.

PANEL MEMBER GLANTZ: But you can particularly step on his toes.

PANEL MEMBER BLANC: Thank you.

Well, I think it's a challenge because here you've got this sort of very large data set of human exposure with a relevant endpoint from a public health context and an interesting biological effect, which I actually wasn't aware of this sort of -- that you could use it, you know, as a poor man's methacholine. I know that you could use sulfur dioxide as methacholine if you wanted. And that's how much more responsive asthmatics are to sulfur dioxide.

You know, you may want to just consult informally with Warren Gold or someone else who -- or Homer Boushey on how you're doing the conversion given how De Vilbiss nebulizers work and what the delivered dose is. Because the delivery dose is actually pretty small, and so maybe you're not as many orders of magnitude higher than you think. I don't know.

PANEL MEMBER GLANTZ: They're both at UCSF.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. We could take a closer look at that. I

realize that we didn't actually even explain why we didn't use these, I don't think. Karen, did we?

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: No.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. So we could describe that.

PANEL MEMBER BLANC: So that at a minimum --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: At a minimum we could do that. And, you know, I'm happy to call Homer Boushey and talk about that.

PANEL MEMBER BLANC: Because in fact the chemistry of acetaldehyde is that it would be in water droplets, wouldn't it? I mean in reality when you --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I know we've had this issue many times. I mean there is a whole bunch of installation studies with diesel exhaust particulate, for example. And it's very hard to say what does that mean in terms of meters -- you know, micrograms per meter cubed? So it's always an issue trying to do that jump -- make that jump.

CHAIRPERSON FROINES: Let's go ahead, unless Paul has more.

PANEL MEMBER BLANC: No, I just -- I think this is something you really should explore and see if it changes -- they may actually just be a great justification for sticking with your eye study. But that sixfold

factor, you may be better able to justify it.

PANEL MEMBER GLANTZ: You know, there's also -- I wasn't going to bring this up. But I will since you're going to be revisiting this event.

There's a fair amount of evidence that acetaldehyde has very strong oxidizing effects that affect platelets and cardiovascular risk too. And Neal Benowitz at San Francisco General has done a bunch of stuff with that. So you might want to just talk to him too. I don't know if the magnitude of the effect -- or the doses are above or below what you're talking about. But it's very long-lived in blood. And, you know, he thinks a lot of the cardiovascular effects of secondhand smoke are due to the acetaldehyde in the secondhand smoke. And he's written some stuff about acetaldehyde and cardiovascular effects or reviews of it or something. But I would also talk to him.

CHAIRPERSON FROINES: But --

PANEL MEMBER GLANTZ: If it turns out that it's no where near as sensitive an endpoint as what you have in there, I wouldn't bother with it. But it might be worth at least checking.

CHAIRPERSON FROINES: But I would argue that -- we're talking right now about a specific issue associated with the acute effects.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes.

CHAIRPERSON FROINES: I don't think there's any question but that acetaldehyde is an important chemical in terms of chronic effects.

PANEL MEMBER GLANTZ: No, but these acute effects could be platelet activation and triggering acute coronary effects.

CHAIRPERSON FROINES: Yeah, but that may occur also as a result of the inflammatory processes in the lung that produce immunologic responses that affect the cardiovascular system. So the mechanism is actually complicated.

PANEL MEMBER GLANTZ: Well, they're probably direct ended. And both of those things are probably going on actually.

I just think since you're going to be looking into this a little more, it's worth checking. And it may be that the acute effects aren't that important or it may be that the levels of exposure required are higher than what you're talking about here, in which case there's nothing to pursue. But I think it's worth just checking.

CHAIRPERSON FROINES: We in our studies have shown the compounds like this produce lung remodeling, produce mucosecretion that produce esophageal contraction.

I mean there are a lot of effects that we've shown from these kinds of compounds that are very relevant to acetaldehyde.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Okay. The key studies for the 8-hour and chronic REL determinations that were used are two studies done by Appelman. The first one was done in 1982 and it was a four-week inhalation study where ten male and ten female rats were used per dose group. They were exposed to 0, 400, 1,000, 2,200, or 5,000 ppm for six hours a day, five days a week.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: A follow-up study done by the same group in 1986, also four-week inhalation study on rats, used male only Wistar, rats ten per dose group, and exposed them to 0, 150 or 500 ppm for six hours per day, five days per week.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: So this is a concurrent derivation of both the 8-hour and chronic RELs, since they were based on the same key studies in rats. And the critical effects was nasal degeneration of olfactory epithelium being the most sensitive endpoint. A LOAEL was determined as 400 ppm and a NOAEL was determined at 150 ppm.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Here is the incidence data for degeneration of nasal olfactory epithelium. And this was shown for each dose group the number examined and the number affected. Shows again that the LOAEL was at 400 ppm, where 16 out of the 20 were affected, and the NOAEL was at 150 ppm, where 0 out of 10 were affected.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: The data also provided individual severity data for each animal. And so we did an analysis of severity by assigning a number that corresponded to the severity level they provided in the study. And the means and standard deviations were calculated based on the severity gradings for all animals in a given dose group.

And this just shows what the severity levels were called by the authors.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: So this shows both the males and females separately. And the data was analyzed both separately and together. And the number of animals in each dose group as well as the mean and standard deviations. This data allowed to use the benchmark dose modeling continuous data as opposed to just

using a dichotomous incidence data analysis.

And just a note, the blank spots are representative of where the one study only used male animals instead of female animals for those 2 dose groups.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: So this table shows the results of benchmark dose modeling for numerous continuous models. And they're all in quite good agreement for the benchmark concentration of 100, 101, and 97. And so a mean was taken of those values.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: And 99 was then -- which is what the mean is, 99 ppm was used as the benchmark dose.

A time adjustment was necessary for a REL determination. And for the 8-hour we used a time adjustment that assumed the 8 hours includes the active waking period when an adult inhales 10 meters cubed of air, which is half the daily total intake of 20 meters cubed.

And it was ingested for the 6 hours to 24 hours and the 5 days a week to 7 days a week. Whereas the chronic time adjustment was only 6 hours per 24 and 5 days per 7.

We used a PBPK model that's recently been

developed and published by Teeguarden, et al. And this was applied to both the 8 hour and the chronic.

This study produced a dosimetric adjustment factor of 1.36. It was looking at the difference between rats and humans for the nasal -- differences in nasal effects. And we used a human equivalent concentration method based on this study.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: So looking at the uncertainty factors we applied for both the 8 hour and the chronic RELs. Because we used a benchmark dose, we did not need a LOAEL uncertainty factor. However, we did need a subchronic uncertainty factor because the four-week study time represented 8 to 12 percent of the lifetime of the animal. So we used a radical 10 for that.

For the interspecies uncertainty factor, a toxicokinetic component, because we had an acetaldehyde-specific PBPK model, we were able to reduce our toxicokinetic uncertainty factor to 1. And we used a default radical 10 for the toxicodynamic for lack of additional information on the toxicodynamics.

For intraspecies uncertainty factors, we used a radical 10 for inter-individual variation in the toxicokinetic component. And toxicodynamic component we used again the 10 for the potential of acetaldehyde to

exacerbate asthma in children.

This yields a cumulative uncertainty factor of 300, which was then applied to both the 8 hour and chronic, which are at different values due to the change in the time adjustment. So for the 8 hour we divided 48.1 ppm, for example, divided by the cumulative uncertainty factor of 300, to yield 150 parts per billion. Whereas, with the chronic we divided 134.6 ppm divided by the cumulative uncertainty factor of 300, to get the 76 parts per billion.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: We did have supporting studies for the 8-hour and chronic REL determination, one being a new study that was recently released by Dorman, et al., in 2008, which was a subchronic study in male rats exposed to acetaldehyde for six hours a day, five days a week for 13 weeks at concentrations of 0, 50, 150, 500, and 1500 ppm.

The LOAEL for this study was determined to be 150 ppm and a NOAEL of 50 ppm for the same endpoint of degeneration of nasal olfactory epithelium.

We attempted to do benchmark dose modeling for the incidence data. And it ran in close agreement with the NOAEL for the study where we had a benchmark dose of 45.3 ppm using a quantal linear model and a benchmark dose

of 48.3 ppm using the probit model. However, statistically these models were not reliable due to the small sample size and the dose spacing. If you look at the table below, you'll see the 150 ppm that was the determined LOAEL for the study versus the 50 ppm of the NOAEL for the study. It jumped from 0 response to 100 percent response.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: So this was -- we went ahead and determined what a REL would look like using this study anyway. So, again, it's Dorman, et al., 2008, which was published in February of '08, using 12 animals per group of rats that were exposed to, again, 0, 50, 150, 500, or 1500 ppm for six hours per day, five days per week, for 13 weeks, with the same endpoint of nasal degeneration of olfactory epithelium. The LOAEL determined was 150 and the NOAEL was 50. We used the dosimetric factor from the Teeguarden PBPK model of 1.36. The time adjustment for exposure was adjusted similarly to the previous derivations, 6 out of 24 hours and 5 out of 7 days.

A LOAEL uncertainty factor of 1 because a NOAEL was given. A subchronic uncertainty factor of radical 10. The exposure was right on the border line of 12 percent lifetime of the animal. A toxicokinetic factor of 1

because of the PBPK model, radical 10 for toxicodynamics as the default because we didn't have interspecies toxicodynamic information.

For the intraspecies we had radical 10 for individual variation for toxicokinetic. And for toxicodynamic, again we used the 10 for potential asthma exacerbation. This yielded a cumulative uncertainty factor of 300, resulting in a reference exposure of 40 PPB, which is about half of what the Appelman data suggested.

However, as I previously mentioned the limitations to this study were that we went from 0 response to 100 percent response. So there's an uncertainty in what the true NOAEL might have been in that study. Also, the length of the study was really on the border between subchronic and chronic. And the severity data that was provided was not adequate to allow continuous benchmark dose modeling like we were able to do for the Appelman study. So we were only able to run dichotomous models. And as I mentioned earlier, those were not statistically significant due to the dose spacing and the 0 to 100 percent response rate.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: They also in the study by Dorman looked at respiratory epithelial

hyperplasia. They found a LOAEL of 500 ppm and a NOAEL of 150 ppm, which is in rather good agreement with the Appelman study NOAEL of 400 ppm -- I'm sorry -- LOAEL.

We did benchmark dose modeling on this data as well. The probit model yielded the best result, with a benchmark dose of 100 ppm, which is in very good agreement with the benchmark dose we came up with with the Appelman study of 99 ppm. Therefore, it is supportive of our REL.

As you can see the data below for this aspect of the study, it still had a low animal number. But there's a slightly more dose response that allowed to do the benchmark dose modeling going from 0 to 1 to 11 to 12.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Another supporting study was done by Saldiva, et al., 1985. While this couldn't be used as a REL determination because it used only one dose of 243 ppm, eight hours a day, five days a week for five weeks, it resulted in intense nasal inflammatory reaction with olfactory epithelium hyperplasia. And the dose of 243 ppm fit right on our dose response curve for our benchmark dose model of the Appelman data between 400 and 150 ppm, which was in between our LOAEL and NOAEL for the Appelman data.

Another supporting study was the Woutersen, et al., chronic study in rats, where rats were exposed to 0,

750, 1500, or 3,000 ppm six hours a day, five days a week, for up to 28 months. And while this was the chronic study that we saw and we did see nasal olfactory degeneration, we were not able to use this because 1) a NOAEL was not determined for this study, and 750 ppm was the lowest dose used. So we would have needed to see lower doses for that one. But it is in support of our key study that we did use.

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OEHHA ASSOCIATE TOXICOLOGIST RIVELES: We did only receive one public comment for acetaldehyde, and that was that we should take a look at the Dorman and Teeguarden studies. They weren't published at the time of our initial public review draft in November. They were released in February in inhalation toxicology. So we did review those and I did incorporate them, both as using the Teeguarden PBPK as a more specific measure of what's going on with toxicokinetics with acetaldehyde, and as well as looking thoroughly at the Dorman data, doing benchmark dose modeling. And it turns out that these are in good agreement with the Appelman data. We felt that the Appelman data was a better -- we were better able to model using benchmark dose modeling. And it was statistically more significant.

That's all.

PANEL MEMBER FRIEDMAN: I have a question.

What are your thoughts about the fact that in the Appelman study there were a couple of animals with nasal degeneration with 0 dose?

And second question related to that is, what do you do with your benchmark model? Do you include those or not?

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Yes, those were included in the benchmark modeling. And we didn't treat it in any particular different way

PANEL MEMBER FRIEDMAN: You know, what do you think -- does that mean that the study is not accurate or --

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: Well, it was 2 out of 40 animals.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So I think it just means that, you know, like many other disease processes, there is a background rate. It's not 0.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: It might be a viral infection of --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That's right.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: All sorts of reasons why --

CHAIRPERSON FROINES: Say that again. Peter was just giving me something.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Oh, it just indicates there's a -- as with most disease processes, there is a background rate, a background incidence of in this case. And Andy pointed out that if the animals got a viral infection, you might see impacts on the nasal epithelium.

PANEL MEMBER BLANC: And since acetaldehyde is a very specific example of a chemical for which we know that there's human genetic variation in its metabolism, how does the uncertainty -- or the square root of 10 adjustment for variation or even the animal to human factor of 10 take into account that -- would we anticipate that someone who was acetaldehyde dehydrogenase deficient would have more of a response?

OEHHA ASSOCIATE TOXICOLOGIST RIVELES:

Teeguarden -- the Teeguarden, et al., study did look at ADLH2 deficient humans and incorporated that into the dosimetric adjustment factor.

PANEL MEMBER BLANC: Which you said was about 3 or something along --

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: 1.36.

PANEL MEMBER BLANC: Is that 1.36, is that a function? Is there a square function or something? It

doesn't sound like very much of an adjustment for a genetic deficiency in metabolizing something.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, it's actually -- the model does not just look at that. It includes other things like flux across the nasal epithelium. So, you know, it's actually a little more complicated than just looking at kinetic aspects.

PANEL MEMBER BLANC: I mean does it -- I guess what I'm asking is mechanistically or mathematically does it just smooth, assuming that some percent would be genetically deficient? Is that what it does? Because that maybe is not exactly the point that --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I think they were doing analysis of various, you know, example model parameters in effect. You know, I don't think it was a population-based model or anything fancy like that. I think they were just using specific parameter values.

One of the things about this is of course that although obviously metabolism does have an influence -- probably, you know, quite a significant influence at one level, we're basically here looking at a point of first contact, impact. So the opportunities for systemic metabolism at least and all these other distributional

processes are considerably reduced. So you're not going to see quite the same range of variability due to metabolic factors that you would be seeing for a systemic effect. The fact of the matter is that, you know, we have allowed for the fact that there is a potential variability there, both in terms of looking at the dosimetric adjustment factor and what the model tells us. And also in incorporating -- can we go back to your table here.

The uncertainty factors we used.

In this particular case we have an intraspecies uncertainty factor toxicokinetic component of square root of 10 here, which is in fact more than we've used in some other cases where we would have a strict point of contact effect with no metabolic contribution.

CHAIRPERSON FROINES: Andy, where's your square root of 10?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: On slide number 14, the intraspecies toxicokinetic uncertainty factor, square root of 10 for inter-individual variation.

PANEL MEMBER BLANC: So people who are acetaldehyde dehydrogenase deficient, relatively speaking, are only three times less efficient -- one-third as efficient. They're not one-tenth as efficient, they're not one-twentieth as efficient at metabolizing?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION
CHIEF SALMON: The supposition is that we've had one-third the impact on the nasal epithelium. We're not talking about how much acetaldehyde --
PANEL MEMBER BLANC: Yeah, but what is the basis of that? I understand that that's what you're doing by default. But what is your biological basis in this particular example?
I'm harping on this a little bit because here we have a very clear example of a very common genetic variant in humans, which I'm sure it wasn't in the test animals that they studied. And it's fine if you tell me that acetaldehyde doesn't exist in nasal epithelium and therefore the metabolism of the chemical doesn't occur in the nose anyway and therefore the effect is -- it's broken down by other effects. Or if you said that there would be mechanistically no reason to expect a greater epithelial irritation with or without acetaldehyde -- I mean I would accept all of those things. But what I'm trying to understand is the rationale --
CHAIRPERSON FROINES: I wouldn't -- I think to assume that in epithelial cells that there is no metabolism is wrong.
PANEL MEMBER BLANC: Well, I --
OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: That isn't assumed. But what the Teeguarden model is saying is that in terms of the localized concentrations reached, the primary driver is the rate of delivery, you know, by atmospheric deposition. And the local metabolism has some influence but not a huge amount. Is that --

CHAIRPERSON FROINES: Yeah, but I think that's the problem that Paul's raised, precisely. It's like -- it's saying, we know that there's very wide variability with respect to that population. I mean that is the ability to handle acetaldehyde so that --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: If the primary determinant is the rate of deposition rather than rate of metabolism, then that variation in metabolism would have a somewhat limited effect.

PANEL MEMBER BLANC: Yes, but -- you know, I know you made that clear from his model. But was there a basis for that presumption in his model? I mean a convincing basis.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, it's asserted to be, you know, a reasonably factual model of what goes on.

PANEL MEMBER BLANC: And by the same token, even if you accepted that, you have a factor of 10 because you

feel that children have more asthma and this is going to therefore be preferentially an issue for exposure in children, right? That's the basis of the 10?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes. I mean there's an issue here in terms of looking at the nasal deposition -- you know, based on the rat study obviously, it's deposition in the upper respiratory tract which is driving the critical response here. But when you go to the human situation, we're also concerned about responses further down the respiratory tract for two reasons: One is that the human nose is a notably less efficient scrubber than the rodent nose. So the fact that you're seeing upper respiratory tract lesions in the rodent fairly exclusively doesn't mean that there won't in addition be lower respiratory tract responses in the human.

CHAIRPERSON FROINES: Andy, that was a question I was going to ask you and Paul, because -- what was done, if anything, in terms of looking at lower respiratory tract?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Well, the Teeguarden model is a nose model. So the answer is that doesn't accommodate that, which is one of the reasons why we have an extra concern about lower respiratory tract responses.

The other issue is that even if your exposure and human response is -- you know, if you can confine your attention to what's going on in the upper respiratory tract. The sensory response is to irritants in humans, include things driven by the central nervous system which affect the lower respiratory tract. I mean in rodents you have this rather simplistic, you know, the RD-50 type response. And that's a fairly simple, you know, effect on the control system.

In the human case your response isn't simple like that. It involves a whole range of things, including -- I think we -- hearing earlier, you know, you do see things like -- secretion and bronchiole responses and coughing and, you know, various other things which actually potentially interact with the kind of problems that you're having as an asthmatic. So the human situation -- and I think what we're saying is it's a lot more complicated and it does include at least notionally the possibility for lower respiratory tract responses. So that's one of the reasons why that uncertainty factor was increased.

PANEL MEMBER BLANC: Well, let me finish with my thought. Actually this is for me to see if I understand how you're doing all these things.

So you have these other studies in humans where it looked at acetaldehyde dehydrogenase and bronchial

hyper-responsiveness with inhalation of acetaldehyde. And those studies showed that there was a different response, or didn't, with acetaldehyde dehydrogenase deficiency?

I mean it says acute -- on page 8 it says, "Another acute human study showed increased sensitivity to acetaldehyde by alcohol sensitive subjects." So I'm assuming -- and then it goes on to detail that. Right?

OEHHA ASSOCIATE TOXICOLOGIST RIVELES: That is correct, whether they were actually diagnosed as being ADLH2 deficient, I'm not sure of that detail, but I can look at the paper.

PANEL MEMBER BLANC: Okay. I mean we could assume that they must have decided that, determined that.

So let's take the hypothetical scenario of a child who happens to be alcohol dehydrogenase sensitive -- deficient. So wouldn't that child -- and on general principles you're saying children are ten times -- we have to be ten times lower to be protective of children with asthma. But that's not being protective of children with asthma who are alcohol dehydrogenase deficient, is it?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: No. That's where the UFH-k comes in where we've got a root 10 --

PANEL MEMBER BLANC: Oh, for the square root of 10.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yes.

PANEL MEMBER BLANC: What is your basis? Was the curve suggestive that the difference was threefold in this study of -- for example, in the study of asthma in the bronchial constriction in the alcohol dehydrogenase sensitive versus non-sensitive subjects?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I don't think it was threefold.

PANEL MEMBER BLANC: Was it less than threefold? I mean I'm hoping it's less than threefold, because --

CHAIRPERSON FROINES: That would be very surprising, don't you think?

PANEL MEMBER BLANC: What?

CHAIRPERSON FROINES: That would be surprising.

PANEL MEMBER BLANC: Well, I don't know. I don't know the study.

CHAIRPERSON FROINES: No, no, I'm saying in terms of that issue, the fact that it would be that limited, it would be surprising.

PANEL MEMBER BLANC: I don't know. I mean you can see where I'm going with this. If it was sixfold, then obviously you --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: You'd need a bigger factor.

PANEL MEMBER BLANC: -- you'd need a bigger factor. This would be one of those examples where in certain cases, you know, we use a bigger number.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Yeah. No, I see where you're going.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, we're looking at a couple of different ways of looking at this. In the papers, it looked like the mean causing a 20 percent decrease in Epi D1 ranged from 18 to 45 depending on the group. So that's within threefold.

We should put that in here if it's in here.

PANEL MEMBER BLANC: Anyway, I don't think you need to -- what I would say is one of two things: Either review the data and say it was about threefold and this supports their use and say that explicitly. Or if it's not and you need to change your number, change your number, I mean, to be consistent.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: It sounds like the threefold is in fact in -- you know, a reasonable ballpark. But we'll tighten up on that, make sure we believe what we see in the paper here.

PANEL MEMBER BLANC: And then say it.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION

CHIEF SALMON: Yes.

PANEL MEMBER BLANC: Mr. Chair?

CHAIRPERSON FROINES: What?

PANEL MEMBER BLANC: When we finish this chemical, can we have our lunch break?

CHAIRPERSON FROINES: Yeah.

I will spend some time on this, because I didn't spend time on it, between now and June.

How do you feel about your -- I mean if you ask yourself where are the concentrations of acetaldehyde in the air, what do you get? What's the ARB data on acetaldehyde?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I think they're a few parts per billion typically. I'm not sure whether -- do we have --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It's in the -- in the South Coast, the annual average was 1.4 parts per billion in '02. But interestingly enough, you get probably more exposure indoors, because there's a lot of indoor sources.

There's been some measurements of U.S. homes and it ranged from 8 to 20 parts per billion. So it's higher in and out.

CHAIRPERSON FROINES: This is one of those issues where we know that -- well, this is one of these issues

that the overall concentration of various types of carbonyls becomes an important issue, because the cumulative exposure to carbonyls is -- if you look at one chemical with the 1.2 part per billion versus a REL of 76, that's -- you want it to be dismissive if you're not careful. But the issue of the carbonyl concentrations in the mix and the potential for chronic effects via number of mechanisms which are becoming clearer as we speak, it raises an important question of how are we going to address that issue in the future.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: One of the things which we commented on in, you know, the ethanol report that we did some years ago was the facts that if you added up the risks -- well, not the risks -- but, you know, the hazard indices for, you know, for the various eye and respiratory irritants, you came up with, you know, a significantly elevated hazard index. So I think it was about three point something for eye irritants and not far short of that for respiratory irritants. And that wasn't looking at the whole range of it, but it was certainly including, say, formaldehyde, acetaldehyde, and acrolein or something like that. So definitely there is a cumulative impact of these carbonyls.

CHAIRPERSON FROINES: You don't think --

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: No, there is -- there definitely is a cumulative impact of these carbonyls.

CHAIRPERSON FROINES: Yeah. So I think we should table this and finish this next month. And go take a lunch break, as Paul is my conscience on breaks.

PANEL MEMBER BLANC: And what time do you want to reconvene?

CHAIRPERSON FROINES: I don't have a watch.

PANEL MEMBER BLANC: It's 12:35.

CHAIRPERSON FROINES: We have -- Craig and I have planes at 3:30. So we're going to have to stop about what, 2 o'clock?

MR. MATHEWS: 2:15, 2:20.

So it's 12:35 --

PANEL MEMBER BLANC: 1:15?

CHAIRPERSON FROINES: It's 12:35 now?

1:15 would be fine.

(Thereupon a lunch break was taken.)

AFTERNOON SESSION

(Thereupon an overhead presentation was Presented as follows.)

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. Now I'm going to hear from Joe Brown on arsenic.

OEHHA STAFF TOXICOLOGIST BROWN: Thank you. Can you hear me?

CHAIRPERSON FROINES: Yes.

OEHHA STAFF TOXICOLOGIST BROWN: Thank you.

Can you hear me?

Okay, good.

(Thereupon an overhead presentation was Presented as follows.)

OEHHA STAFF TOXICOLOGIST BROWN: The first two slides here on arsenic are generally overview slides.

The acute REL of 0.2 micrograms of arsenic per meter cubed is based on developmental effects in mice. These are a decrease in fetal weight.

This is the same study and derivation as the current aREL of 1999. Essentially we could not find or locate a better study than this.

And the other issue in here is that we decided to take the same derivation as before with a one 1,000-fold uncertainty factor. And the reason for this is that this

particular study involved four-hour exposures on four successive days during a gestation in mice. And we couldn't really make a temporal adjustment on this. We didn't feel that we were justified in doing that. And so partly on this basis -- and this is sort of a judgment call -- we decided to stick with the current 1,000-fold uncertainty factor for lack of a NOAEL intraspecies and inter-individual variation.

So that's it on the acute REL.

Now, the 8-hour and chronic RELs are the same. And .015 micrograms of arsenic per meter cubed. And this is based on decreased intellectual function in exposed children. And I have slides on that further on down.

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OEHHA STAFF TOXICOLOGIST BROWN: Another interesting fact here is that while we reviewed all of the data on arsine and actually analyzed the data and came up with some provisional values, some provisional potential RELs for arsine, in the final analysis we felt that the data was so poor, we just didn't have enough confidence in it to use any of these data. So we decided to include arsine under the values for inorganic arsenic, because we felt those would be sufficiently protective also of arsine exposure. So that's another wrinkle in this particular assessment.

Finally on this overview slide, despite the fact that we're using critical studies in susceptible age groups, we're also adopting a cumulative UFH of 30 to account for kinetic and dynamic uncertainties. There's been an awful lot of research on arsenic. Recently you can hardly go through a week without finding a new paper in this area. And we feel there's still a substantial uncertainty with respect to mode of action for individual non-cancer endpoints and even the metabolism, particularly polynucleotide -- or polymorphisms for arsenic metabolism genes in particular.

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OEHHA STAFF TOXICOLOGIST BROWN: Now, the inorganic and 8-hour chronic RELs. The critical study that we selected is Wasserman, et al., from 2004. This is arsenic exposure by the drinking water route. 201 children -- 10-year old children were studied. And they reported a decreasing intellectual function versus arsenic concentration in water. And this particular data set could be fit to a quadratic regression. And I derived a slope off that regression of minus .43 points per microgram per liter.

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OEHHA STAFF TOXICOLOGIST BROWN: I used that slope to estimate a particular value of 2.27 Micrograms of

arsenic per liter, or one point decrement. And at one liter a day, this is also 2.27 micrograms of arsenic per day.

And then I converted that to an inhalation-based value, assuming 9.9 cubic meters per day inhalation rate, a 50 percent absorption by the inhalation route for arsenic. And --

PANEL MEMBER FRIEDMAN: May I interrupt with a question?

OEHHA STAFF TOXICOLOGIST BROWN: Sure.

PANEL MEMBER FRIEDMAN: On the previous slide where you have the decreasing intellectual function, minus 0.443 points per microgram, you have R squared equals 1.0. I've never seen an R squared like that. Are you saying that things fit perfectly on that regression line?

OEHHA STAFF TOXICOLOGIST BROWN: That's exactly what I'm saying.

PANEL MEMBER FRIEDMAN: Wow. Okay. I just had never seen that before.

OEHHA STAFF TOXICOLOGIST BROWN: We're using a UF of 30 here. It's 3 --

CHAIRPERSON FROINES: The one liter per day?

OEHHA STAFF TOXICOLOGIST BROWN: Yes, one liter per day in children.

CHAIRPERSON FROINES: Oh, in children.

OEHHA STAFF TOXICOLOGIST BROWN: And if you look at the document, we have some different values in there, slightly higher for children -- drinking water in California children. But this is sort of a default, and we thought it would probably be better -- it's probably actually more health protective to stick with the one liter per day per children in this particular age group.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: The children in question are 10-year old children?

OEHHA STAFF TOXICOLOGIST BROWN: Yeah, they're 10-year old children. They're in Bangladesh obviously, and it's pretty hot there.

As I said, we're using UF age of 30. It's 3 for pharmacodynamic and 10 for pharmacokinetic differences. And we could calculate the cREL based on this particular study by dividing the 2.27 per day by 9.9 cubic meters per day, 30 for UF and .5 for absorption.

Now the absorption figure of 50 percent is a default. But actually there's some data to support this. In children, we looked at the ICRP, a lung model for children for reparable particles. And they give values depending on inhalation rate of 42 to 52 percent deposited for reparable particles. And there's also a study cited in the document by Votter, et al., on occupational

exposure, where she looked at urinary excretion and calculated a value of 42 percent excreted. And that similarly was absorbed through the inhalation pathway.

I estimated 52 percent by my own calculations on her data set. So, you know, 42 to 54 percent, the 50 percent default that we think is reasonable.

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OEHHA STAFF TOXICOLOGIST BROWN: Now, there's also a key supporting study here, Tsai, et al., 2003. And these are different endpoints but related. A study of cognitive development in 49 13-year old children, also exposed to arsenic through drink water root.

They did four developmental tests. These are computer-based studies based on how long they could study the children. These were school children they were looking at. Now, there were three groups identified less than .15 parts per billion, arsenic and water as a control, 131 and 185 as the two dose groups. And they found significant dose responses on three of the four tests - the continuous performance test, the pattern memory test, and the switching attention test. The most sensitive of these was the switching attention. And we were able to analyze the data and getting benchmark dose at the 5 percent level of 19.7 parts per billion. Or if you looked at it in terms of cumulative arsenic intake

over the approximately 10 to 11 years of exposure, that is 25.4 milligrams for cumulative intake of arsenic.

So if we base a calculation on the ten years intake, assuming one liter a day, ten cubic meters a day, 50 percent absorption, 30 UF, we can also calculate a comparable cREL of .046 micrograms per cubic meter, or .05 rounded.

--o0o--

OEHHA STAFF TOXICOLOGIST BROWN: Some of the issues raised in the comments that we received: Andy's already mentioned the UFH. And people thought that for arsenic probably 10 was sufficient. And I think again we believe there still are outstanding uncertainties of absorption, distribution, metabolism, and excretion of arsenic in children that justifies the use of a higher value for the kinetic subcomponent of UFH. And we think 10 is the value to use here.

A number of studies indicate human variability in arsenic toxicity is related to genetic polymorphism, some arsenic metabolism genes, and more data is needed. There's actually a study cited in the document. And these -- well, that for one of these enzymes, they found a substantial difference in different groups of children in Mexico. And there are other studies, not in children but in adults, indicating polymorphisms essentially broadening

the range of human sensitivity to arsenic metabolism, essentially affecting the methylation capacity, which seems to be related to some of the endpoints, although not specifically the endpoint we're studying here. We don't have data for that yet.

--o0o--

OEHHA STAFF TOXICOLOGIST BROWN: Another comment we received was that the key studies for the 8-hour and the cREL are based on drinking water studies and not inhalation.

Well, inorganic arsenic is known to act similarly by the oral or inhalation exposure. An example is lung cancer, which is caused by both inhalation and ingestion of inorganic arsenic.

We believe oral studies are relevant, and we have no suitable inhalation study for a quantitative analysis of these neural developmental endpoints.

Inhalation of our airborne arsenic is probably going to occur in a particulate form. And it's always going to involve some swallowing of these particles through mechanical removal into the upper airways and then swallowing. So there's going to be some oral component even to inhalation of airborne arsenic particles.

--o0o--

OEHHA STAFF TOXICOLOGIST BROWN: Another comment.

Why was the Wasserman study used when others gave higher values.

Well, the Wasserman study gives a value of .015 micrograms per cubic meter. And it's supported by the Tsai study, as we said, a .046. That's a difference of threefold. And we felt that rather than derive a mean of two or more studies, we chose to use the most health protective study of the most serious and adverse effects seen in children.

You know, on occasion we have used means in the past. But there are four things that we thought were comparable. And, you know, currently I think more recently we've tried to focus on the most sensitive --

CHAIRPERSON FROINES: Can I ask you a question, Joe?

OEHHA STAFF TOXICOLOGIST BROWN: Sure.

CHAIRPERSON FROINES: Going back to this issue of oral versus inhalation. Are there any studies in the literature that looked at the relative systemic uptake of inhalation versus oral ingestion?

OEHHA STAFF TOXICOLOGIST BROWN: Well, I mentioned the study with water, which was in smelter workers. And they calculated the value -- or estimated value at 42 percent. Higher values are seen by the oral route. We generally assume complete absorption of --

CHAIRPERSON FROINES: I can't hear you.

OEHHA STAFF TOXICOLOGIST BROWN: I said we generally assume complete absorption of oral inorganic arsenic. In animals it's -- I think it's well over 70 percent, depending upon the form and, you know, what it's given with.

Certainly there would be less taken up by the inhalation route than the oral route. The question is, how much less? You know, our defaults are 50 and 100 percent respectively according to inhalation and oral.

Does that answer your question?

You know, the data is not that great. I mean, as I said -- and I made my own estimate on Fawer's data. I took four of her subjects and assumed ten cubic meters per day during the workday, one liter per day of urinary excretion, and I got 52 percent on four subjects. This was their -- she followed the workers through the week, measured airborne arsenic. It wasn't specified as to particle distribution, so we don't know about that. But we know it was in the air, it was measured. And she followed it the year and it was more or less study, study, looking at the grass -- over the week. So she was more or less a sort of study, study situation where they were breathing it in every day and it was coming out every day in the urine.

So those are the --

CHAIRPERSON FROINES: She's a good scientist. So it's --

OEHHA STAFF TOXICOLOGIST BROWN: It would be great to have more data. But, you know, it's difficult to get volunteers to take this stuff.

Okay. We had another comment here.

You know, comparing our values with other values, that the Netherlands' Public Health & Environment, they developed a level, a tolerable concentration in air of one microgram per cubic meter for cancer and non-cancer effects. And this was, as the commenter said, nearly two orders of magnitude higher than our value.

And I guess -- you know, I guess we would say we just don't agree with -- I don't know how old this particular assessment is anyway. But I think in our view the risks of arsenic exposure have been historically underestimated for both cancer and non-cancer endpoints; one reason being the lack of suitable animal models for arsenic-related disease.

I don't think EPA has a comparable value for non-cancer for arsenic.

CHAIRPERSON FROINES: Well, OSHA standard is ten micrograms per cubic meter.

OEHHA STAFF TOXICOLOGIST BROWN: It's difficult

to say. You know, there's so much new stuff coming out on arsenic. As I said before, it's like a growth industry, arsenic research, right now. And, you know, I've got a database of over 1400 articles on my computer at home.

CHAIRPERSON FROINES: I was at a meeting last week with Allen Smith, and he has all sorts of work coming out. And there's a very good review of arsenic toxicology and -- by a fella named Yoshito Kumigai, who wrote a review in the annual review of -- is it Pharmacology and Tox -- it's Toxicology and Pharmacology -- in the last couple years. You might not have found it. It's quite good.

OEHHA STAFF TOXICOLOGIST BROWN: I'm updating my database all the time. But it's possible I missed something. People are sending me things all the time, but I catch some, I miss others.

That's the final slide I have. I didn't want to overdo this. The document is quite lengthy. I basically wanted to hit the highlights of this.

And we took comments from Gary Friedman and adopted most of his suggestions and responded point by point. So I think you got that to --

PANEL MEMBER FRIEDMAN: I didn't see the response point by point. You're just saying that it's just in the document?

OEHHA STAFF TOXICOLOGIST BROWN: No. I actually -- I don't know why you didn't receive it.

PANEL MEMBER FRIEDMAN: I never got it.

OEHHA STAFF TOXICOLOGIST BROWN: I assume -- I made point-by-point responses and I passed them up the line.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I'll have to check on that. I thought we sent those.

PANEL MEMBER FRIEDMAN: Well, this document that we received on April 2008 with I guess is a modified -- is this your final report, this report?

OEHHA STAFF TOXICOLOGIST BROWN: Not necessarily final. But it should include responses I made to your comments and any others I received that --

PANEL MEMBER FRIEDMAN: Oh, okay. So that's the next thing I should be reviewing?

OEHHA STAFF TOXICOLOGIST BROWN: Yeah, you should take a look at that. And also you should get my point-by-point responses to your comments. But I did go through them. I spent a lot of time answering them.

PANEL MEMBER FRIEDMAN: One thing I just today was flipping through looking for my suggestion that there be a glossary of all these abbreviations. Did that ever show up in anything --

OEHHA STAFF TOXICOLOGIST BROWN: That's in the appendix.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We have a glossary in the appendix.

OEHHA STAFF TOXICOLOGIST BROWN: One of the answers was that you should look at the appendix because that's our glossary. But we did go through and add more explanations and tried to dejargonize as much as possible.

PANEL MEMBER FRIEDMAN: Oh, thank you.

OEHHA STAFF TOXICOLOGIST BROWN: So that was done.

PANEL MEMBER FRIEDMAN: Overall I thought it was, you know, a well done report. But most of my concerns were about clarification and what critiques of some of the studies quoted as to whether, you know, you --

OEHHA STAFF TOXICOLOGIST BROWN: But you had a couple of numerical comments in there which I responded to.

PANEL MEMBER FRIEDMAN: Oh, good.

OEHHA STAFF TOXICOLOGIST BROWN: So you'll need to look at those. But I also clarified one in the text. So as you go through the -- as you go through that, you shouldn't see the same sort of questions jumping up at you because I actually did make an effort to respond to your questions.

PANEL MEMBER FRIEDMAN: Okay. And, Andy, will you forward to me the responses?

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: Sure.

CHAIRPERSON FROINES: So, Melanie, did -- I don't want to take up more than a minute or two on this. But if I remember correctly, the cancer number is .007 parts per billion, and this is clearly quite different. So that in terms of looking at arsenic, what's the sort of relationship between that very, very conservative value for cancer relative to the non-cancer RELs?

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, I think it --

CHAIRPERSON FROINES: I'm not sure the question I'm asking --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, when somebody does a risk assessment of a source of arsenic, they're going to have to look at both non-cancer and cancer. So they would use the universal factor for arsenic. And we will actually talk a little bit about arsenic in our upcoming revision of the cancer risk methodology, because it's an example where recent data from Allen Smith actually shows that in utero, in early childhood exposure results in higher relative risks for lung cancer in actually relatively young adults. So

it's a great example of a chemical that's a carcinogen, and the carcinogenicity -- the carcinogenic potency is worse from early life exposure.

PANEL MEMBER BLANC: Can you clarify again for the key dose response that you used, which was the drop-in IQ per water concentration? Can you go back to what the water concentration was.

OEHHA STAFF TOXICOLOGIST BROWN: 2.27 micrograms of arsenic per liter.

PANEL MEMBER BLANC: Would lead to a --

OEHHA STAFF TOXICOLOGIST BROWN: -- to a decrement of one point.

PANEL MEMBER BLANC: So one thing you might want to do by analogy -- going to your study of lung function decrement that's on page 24. You show that there is a 45 ML decrement per 100 micrograms per liter or a 4.5 ML per 10 or a 1 ML for 2.3 or something. So --

OEHHA STAFF TOXICOLOGIST BROWN: And what are you driving at? What's the point of comparing --

PANEL MEMBER BLANC: Well, you're saying that there is this -- I would say that there's a supportive similar health effect to the similar dose response. I mean I don't know what -- I suppose I'd rather lose an ML of lung function --

OEHHA STAFF TOXICOLOGIST BROWN: It's hard to

look at a one point loss in a small study. But if you look at a population, a one point loss could be significant.

PANEL MEMBER BLANC: Well, If you look at a population of 1 ML loss per year -- I mean I don't know what it would be, you know, but --

OEHHA STAFF TOXICOLOGIST BROWN: Yeah, that's an interesting point. I'll have to look at the --

PANEL MEMBER BLANC: So that's just a -- I mean just -- in fact, it's not -- one from an occupational point of view wouldn't have thought that central nervous system toxicity would necessarily have been your target organ of toxicity -- your non-cancer target organ of toxicity for arsenic. So I think it would be nice to back it up with something else.

I'm quite confused as to why section 6.2.3 is -- what it is, where it is. Can you explain that?

On page 27, lung effects. I wonder if this was left over from something else.

OEHHA STAFF TOXICOLOGIST BROWN: You know, the document was rearranged a few times and -- if you have a suggestion --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: It's because it's in infants and children.

PANEL MEMBER BLANC: But this is studies of

adults and cancer risk and mortality. I mean --

OEHHA STAFF TOXICOLOGIST BROWN: Lung effects and --

PANEL MEMBER BLANC: And it's cancer and it's --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: I don't know what you guys are looking at. The one I'm looking at it says chronic toxicity, infants and children, 6.2 and 6. --

PANEL MEMBER BLANC: Yeah, I know. And then in that if you go to page 27, the section on lung effects --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Oh, that's a good style. Allen Smith talks about bronchiectasis as well as lung cancer. So did we not put the bronchiectasis in here?

PANEL MEMBER BLANC: No, bronchi -- and that was going to be another point -- is I didn't see the bronchiectasis studies. Maybe I missed it.

Oh, there's the bronchiectasis. And that wasn't a childhood effect.

CHAIRPERSON FROINES: It's on page 28.

PANEL MEMBER BLANC: That was an adult's, wasn't it

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, yeah, the bronchi -- well, actually what they did was look at -- they were able to separate out

people who had been exposed to very high amounts in utero in early childhood from those who were not exposed to those same high amounts and looked at the risk of bronchiectasis in young adults.

PANEL MEMBER BLANC: But they both had it.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, the in utero and early childhood exposures had higher SMRs for bronchiectasis than the -- if that exposure had not occurred.

PANEL MEMBER BLANC: I see.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: So it was sort of -- he was looking at the period of exposure. Because they had very high concentrations of arsenic in their drinking water and then they actually did something about it and it dropped.

PANEL MEMBER BLANC: This is the chili thing. But then what about the -- but he's also co-published on bronchiectasis from Bangladesh. So then at least that should have been in the other section on lung disease. And I don't see why the lung cancer part that precedes it is so relevant then.

OEHHA STAFF TOXICOLOGIST BROWN: Well, only because it was part of the same study, think --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, it was part -- I mean we can, you know,

de-emphasize that.

OEHHA STAFF TOXICOLOGIST BROWN: If you'd just match it, it would seem like it's coming out of blue. It's sort of an introduction to --

PANEL MEMBER BLANC: All I did was I read it.

OEHHA STAFF TOXICOLOGIST BROWN: Okay. So we need to think about --

PANEL MEMBER BLANC: And I think that the first author on the Bangladesh bronchiectasis was Steinmass.

I mean you should ask Craig. Has Craig looked at this section for you?

OEHHA STAFF TOXICOLOGIST BROWN: I don't know.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Well, we sent it to his branch. Whether they asked Craig to look at it or not, I don't know. But he can ask him to look at it.

OEHHA STAFF TOXICOLOGIST BROWN: It might be bureaucratically impossible.

OEHHA DEPUTY DIRECTOR ALEXEEFF: We can have him look at it.

OEHHA STAFF TOXICOLOGIST BROWN: I know he's sympathetic to it.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. I know that there are some new studies poised to come out in animals, looking at lung development

and arsenic exposure. So if it comes out soon enough, we'll add that too.

OEHHA STAFF TOXICOLOGIST BROWN: That's almost like a moving target.

PANEL MEMBER BLANC: No, I know. But this other thing I mean you could do right away in terms of just the lung that --

OEHHA STAFF TOXICOLOGIST BROWN: If it's already out there, we can look at it and do it.

PANEL MEMBER BLANC: Yeah.

PANEL MEMBER GLANTZ: Are we going to do mercury now?

CHAIRPERSON FROINES: Unless there are other questions on arsenic.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Okay. If the Panel's ready, we can move on to mercury. And we thought we would do mercury today because Dr. Byus was the lead. So if that makes sense.

PANEL MEMBER BYUS: As long as we get Dr. Byus on his airplane.

(Laughter.)

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: That would leave acrolein, formaldehyde and manganese for the next meeting.

CHAIRPERSON FROINES: We've got about 20 minutes.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Twenty minutes. Okay.

OEHHA STAFF TOXICOLOGIST WINDER: Okay. I'm Bruce Winder with OEHHA.

Again, I'll present the overview slides here.

(Thereupon an overhead presentation was Presented as follows.)

OEHHA STAFF TOXICOLOGIST WINDER: The acute REL for the mercury study was based on central nervous system disturbances in pups of rats that were exposed during pregnancy. The 8-hour REL is -- and that acute REL is .6 micrograms per meter cubed. The 8-hour REL is .06 micrograms. And the chronic REL is .03. Now, both the 8-hour and the chronic RELs are based on neurotoxicity in adult humans.

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OEHHA STAFF TOXICOLOGIST WINDER: The acute REL is an animal study. I could find no acute studies in humans.

In this case, as I mentioned, the rats were exposed through the mother in utero. And this was to a mercury vapor level of 1.8 mg per meter cubed for one or three hours per day during gestation days 11 through 14 and 17 through 20.

Then the endpoint here are neurobehavior in the

pups, measured at 3 months and again at 14 months. And they're looking at things like general locomotion, rearing, total activity, performance in a swim maze, this sort of thing.

Now, this study used basically just the two levels, 1.8 mg either one hour per day or three hours per day. So LOAEL study is the 1.8. And for this conversion from the LOAEL to the NOAEL we used the UFL of 10 as being a severe endpoint.

We also included an interspecies toxicokinetic factor of square root of 10 for individual variability. This is for the toxicokinetic effects.

However, for the toxicodynamic effects we're using the larger UF of 10. The idea here is this addresses the greater susceptibility of humans during development to the neurotox. And this 10 is also supported by some data comparing rats, mice, and humans in terms of -- this is in vitro study -- looking at the susceptibility of these cells to mercury exposure. In this case humans tended to be about tenfold more susceptible.

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OEHHA STAFF TOXICOLOGIST WINDER: Now, here again we have the intraspecies toxicokinetic factor of the square root of 10, because the study was performed in

young animals. So we figured, well, we don't need the adult to young conversion.

Similarly for the toxicodynamic effect we're using the square root of 10. This gives us a total cumulative UF of 3,000, which put it right at that limit that we were thinking about. And then the result in the acute REL is .6 micrograms per meter cubed, or .07 parts per billion.

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OEHHA STAFF TOXICOLOGIST WINDER: Now, for the 8-hour and the chronic studies, these RELs are based on several studies out of Piikivi's lab. This is an occupational study, again looking at neurotoxicity in adult males. This includes everything from sleeplessness to memory problems, et cetera.

Now, the LOAEL for this study was 25 micrograms per meter cubed. And, again, because of the severity of this endpoint, we use a LOAEL to NOAEL conversion of 10. And we're adjusting the time for exposure here, the 25 micrograms per meter cubed by the days per week for a seven-day week. Gives us a time adjusted exposure about 18 micrograms per meter cubed.

Now, part of our thinking here is that with mercury the clearance of mercury from the body is pretty negligible day to day. So we expected there's -- where

it's chronic or 8-hour study there would be very little clearance here.

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OEHHA STAFF TOXICOLOGIST WINDER: Now, we use an interspecies uncertainty factor of 1 since this is a human study. The toxicokinetic intraspecies, this is square root of 10. We don't expect a substantial difference among individuals there.

But the toxicodynamic effect we go for the full 10 because again we're expecting a higher level of susceptibility for neurodevelopmental exposures.

So for our 8-hour study, a cumulative UF of 300, for an 8-hour REL of .06 micrograms per meter cubed

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OEHHA STAFF TOXICOLOGIST WINDER: So same set of studies when it's applied for the chronic REL. Again, the same neurotoxicity endpoint. LOAEL is the same.

And the time adjustment here involves this breathing rate that was introduced to some of the others of 10 cubic meters during a workday for a full day.

So this gives us an adjusted value of 9 micrograms per meter cubed.

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OEHHA STAFF TOXICOLOGIST WINDER: Again, it's an interspecies. You have 1 because it's a UF study.

Toxicokinetic effects, again square root of 10 and toxicodynamics 10 again for the greater newer developmental susceptibility.

So our -- it says 8-hour. But that should say chronic REL is .03.

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OEHHA STAFF TOXICOLOGIST WINDER: Now, some of questions -- or some of the issues that were raised with this in the comments, there was some concern that the uncertainty factors that we applied didn't adequately address the developmental data gaps. And they're suggesting that we either add a data gap uncertainty factor and/or toxicodynamic UF of 10. Well, now, in fact we did use a UF of 10 for our intraspecies toxicodynamic factor with this sort of thing in mind.

So, again, we take that as addressing the issues of this uncertainty with respect to neuro development.

The acute REL was a developmental toxicity in rats, so there was no increased UF for that one, because these after all are developmental study.

Neurotoxicity of elemental mercury we think is approximately equivalent to that of methyl mercury with respect to age-related differences in terms of susceptibility. And now there are likely differences in terms of toxicokinetics. But given what we expect to be

the similarity between both elemental and methyl mercury effects, we didn't think an additional database deficiency factor was necessary

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PANEL MEMBER BLANC: I'm sorry, if I caught that correctly. So what you're saying is that the methyl mercury database, which is more robust, suggests that developing -- that the developing human or developing mammals are three times as sensitive as adult experimentally exposed? Is that what you're saying?

OEHHA STAFF TOXICOLOGIST WINDER: I think that's a fair assertion, yes. And that based on the similarity between the two, using that methyl mercury, the database, you'd say that we expect in this circumstance to have a similar kind of --

PANEL MEMBER BLANC: Is that what the data from Minamata suggests in terms of human methyl mercury? I would have characterized the gap as being more than threefold.

OEHHA STAFF TOXICOLOGIST WINDER: Yeah, that's a point. I would guess somewhere in the neighborhood of 3 to 10.

PANEL MEMBER BLANC: Well, 3 to 10 is not 3.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Except for when we use a 10 on the chronic. We

use a 10 for intraspecies toxicodynamics on the chronic.

PANEL MEMBER BLANC: I thought you used human data for the chronic, not animal data.

OEHHA STAFF TOXICOLOGIST WINDER: That's true.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yes, adult human data. So we did -- I'm just responding to your thinking about what the difference in toxicity was if there was congenital Minamata versus what happened to the adults in that setting.

PANEL MEMBER BLANC: Yeah.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah. So, you know, the factor we used here was --

PANEL MEMBER BLANC: Not for the acute. I'm talking about neurologic effects generically. It's a neurologic endpoint if you're using for everything, right?

OEHHA STAFF TOXICOLOGIST WINDER: That's right.

PANEL MEMBER BLANC: You've got a neurologic effect for the chronic. You're using chloralkali worker data from Finland.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Right.

PANEL MEMBER BLANC: And you're using the square root of 3 and square root of 3 for the pharmacodynamic and pharmacokinetic adjustments.

OEHHA STAFF TOXICOLOGIST WINDER: Now, you're talking about for the acute?

PANEL MEMBER BLANC: No, the chronic.

OEHHA STAFF TOXICOLOGIST WINDER: For the chronic. Okay.

PANEL MEMBER BLANC: Craig, am I on target with this?

PANEL MEMBER BYUS: I think so.

OEHHA STAFF TOXICOLOGIST WINDER: We've got the square root of 10 for the toxicokinetic -- a full 10 for the toxicokinetic.

PANEL MEMBER BLANC: You are using for the chronic?

OEHHA STAFF TOXICOLOGIST WINDER: Yes.

PANEL MEMBER BLANC: Okay, good.

Okay. I missed that. Sorry.

So you're assuming that the 10 -- but then let me ask the same question. Does the Minamata data, for example, say that it's 10 or is it worth more than 10? Is it a hundredfold? What do the data --

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: Yeah, I'm not sure we have a good quantitative handle on the Minamata data. You'd have to have pretty good exposure estimates for in utero, perinatal, and adults.

OEHHA DEPUTY DIRECTOR ALEXEEFF: George Alexeeff.

We have looked at the data from -- there was an Iraqi poisoning of methyl mercury. And there's been extensive studying of Seychelle Islands and the Farrell Islands. And so we have looked at that. And U.S. EPA concluded and we concluded that basically the differential between adults and children or pregnant women or fetuses is threefold based upon looking at those endpoints. And that's how all of our reference levels are developed for like us and U.S. EPA for -- and the Natural Academy of Science has also looked at it as well for a fish consumption of mercury. That seems to be how --

PANEL MEMBER BLANC: So, therefore, the 10 is even conservative because you could have argued to use 3 for the pharmacodynamic?

OEHHA STAFF TOXICOLOGIST WINDER: The methyl mercury is -- here we have a difference in the route of exposure. And inhalation of developmental mercury is fairly rapid in efficient uptake compared to ingestion. So that's another reason for considering the 10 versus the 3.

PANEL MEMBER BLANC: I just want to make sure I understand what you're doing.

--o0o--

OEHHA STAFF TOXICOLOGIST WINDER: We also had

comments suggesting that our RELs were lower than so-called comparable values from ATSDR and U.S. EPA for MR RELs, the reference concentrations in the AEGLs.

Well, now AEGLs are values that are derived for typically once-in-a-life-time emergency and short-term exposures. We're trying to develop RELs here to protect health after potentially repeated or long-term exposures.

So these two numbers are really not comparable enough designed to treat the same sort or exposure scenarios.

And the MR RELs and the RfCs are also developed without a particular consideration of children or other, you know, specifically susceptible populations. And these things have been developed and they don't -- the stories won't reflect their most recent science receiving this.

--o0o--

OEHHA STAFF TOXICOLOGIST WINDER: It's also mentioned that the acute REL is only two, threefold higher than the U.S. EPA's ATSDR chronic values. And the commentators expected that our short-term values would be much higher than the chronic. Well, what's happening here is they're trying to compare our values with what the U.S. EPA has derived for their chronic And as we've mentioned previously, it's not appropriate to try and compare this to AEGLs or RfCs. However, we agree that you would expect

the acute exposures to be higher. And when you compare our proposed acute REL, it is twentyfold higher than the proposed chronic REL. So we don't see a conflict there.

--o0o--

OEHHA STAFF TOXICOLOGIST WINDER: It says the cumulative certainty factor of 300 seems far too high for an 8-hour REL since the critical study is in humans.

Well, the reason for this is that, as I mentioned, there's the LOAEL to NOAEL uncertainty factor of 10 because of the severity of the effect, the intraspecies toxicokinetic factor of square root of 10. This is default for inter-individual variability. We didn't expect this to be particularly high in terms of toxicokinetics between adults and -- populations.

The intraspecies toxicodynamic factor of 10, this again because of the developmental susceptibility. So when this is all put together, this comes to the three -- totals.

And that's the end of those.

CHAIRPERSON FROINES: Craig, do have any comments?

PANEL MEMBER BYUS: I thought it was very well written. I mean really did a nice job pulling all the different data together in a nice easy to, you know, read form. You laid out your arguments very nicely. It was

nice. I had a few minor little comments here and there. I'll just -- one of them is, what is the parallelogram approach to doing --

OEHHA STAFF TOXICOLOGIST WINDER: Oh, that --

PANEL MEMBER BYUS: On page 14. Lowendowski, et al., used a parallelogram approach to analyze in vivo/in vitro data and responses of rats, mice, and humans, methyl mercury. I have no idea what that is.

OEHHA STAFF TOXICOLOGIST WINDER: It's a -- let me see if I can dig out the paper here.

It's a method of examining the LOAELs and NOAELs for, in effect -- again, this was done -- this is an in vitro study of human cell, rat cells, mice cells -- to look at the effect where they're seeing the NOAEL and LOAEL for each of those species. And they're finding that the -- for the humans this effect was that it seemed a tenfold lower approximately than in the rats and mice.

PANEL MEMBER BYUS: Where does the parallelogram come in?

OEHHA STAFF TOXICOLOGIST WINDER: It's a way of presenting the data.

PANEL MEMBER BYUS: Okay. I have a few other minor little things like that.

AIR TOXICOLOGY AND EPIDEMIOLOGY BRANCH CHIEF MARTY: We should explain that better.

OEHHA STAFF TOXICOLOGIST WINDER: Okay. So perhaps some explanation of that.

PANEL MEMBER GLANTZ: That's as opposed to the trapezoid.

(Laughter.)

PANEL MEMBER BYUS: Yeah, that's what I'm thinking. There'a a square or the triangle approach. I couldn't understand why it was a parallelogram.

PANEL MEMBER GLANTZ: At least it wasn't circular.

(Laughter.)

PANEL MEMBER BYUS: Yeah, that's good.

PANEL MEMBER BLANC: So the problem with using NHANES data, the mercury values or the equivalent national data is because you can't tease out what is methyl mercury versus what is elemental mercury, is that the problem with that?

OEHHA STAFF TOXICOLOGIST WINDER: Yeah, I don't think NHANES's going to discriminate the speciation there.

And there's only blood; there isn't blood and urine available?

OEHHA STAFF TOXICOLOGIST WINDER: On NHANES' mercury? I'm not sure about that.

There's definitely blood, but I don't know if there's any mercury --

PANEL MEMBER BLANC: Because isn't one of them reflective of inorganic mercury more than --

OEHHA STAFF TOXICOLOGIST WINDER: That I'm not sure.

OEHHA AIR TOXICOLOGY AND RISK ASSESSMENT SECTION CHIEF SALMON: I think that all depends on what the time scale is that you're looking at. I think the long term it will come out in the urine. But, you know, there's a definite time scale issue as to when you're looking at urine versus blood levels.

But in the very long term obviously everything gets -- you know, gets oxidized and winds up in the urine. But that's -- you know, that's in the long term, anything up to 30 years sort of thing.

CHAIRPERSON FROINES: Is somebody driving?

PANEL MEMBER BYUS: Will somebody drive us?

CHAIRPERSON FROINES: We have to stop.

PANEL MEMBER BLANC: Okay. Bye.

PANEL MEMBER GLANTZ: I thought you had to go.

PANEL MEMBER BLANC: I move that we adjourn.

CHAIRPERSON FROINES: Thank you.

Second?

PANEL MEMBER GLANTZ: Second.

CHAIRPERSON FROINES: All in favor?

(Ayes.)

CHAIRPERSON FROINES: Thank you.

(Thereupon the California Air Resources Board, Scientific Review Panel adjourned at 2:14 p.m.)

CERTIFICATE OF REPORTER

I, JAMES F. PETERS, a Certified Shorthand Reporter of the State of California, and Registered Professional Reporter, do hereby certify:

That I am a disinterested person herein; that the foregoing California Air Resources Board, Scientific Review Panel meeting was reported in shorthand by me, James F. Peters, a Certified Shorthand Reporter of the State of California, and thereafter transcribed into typewriting.

I further certify that I am not of counsel or attorney for any of the parties to said meeting nor in any way interested in the outcome of said meeting.

IN WITNESS WHEREOF, I have hereunto set my hand this 23rd day of May, 2008.

JAMES F. PETERS, CSR, RPR
Certified Shorthand Reporter
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